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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 27 1951

THE VITAMIN B_{12} GROUP OF FACTORS

BY

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(From the Research and Development Division, Glaxo Laboratories Ltd., Greenford, Middlesex)

Progress in the vitamin B_{12} field has been so rapid that it seems already appropriate to supplement the review published in the *Journal* a year ago (Lester Smith, 1949). In particular, it has been found possible to obtain in crystalline form two further members of the vitamin B_{12} group of factors—namely, vitamins $B_{12}c$ and $B_{12}d$—as recently announced by workers in these laboratories (Anslow *et al.*, 1950). These factors have been submitted to extensive clinical trials, which form the subject of other papers in this issue.

Characteristics of the New Factors

These new factors were isolated from *Streptomyces griseus* fermentation liquors and were separated by partition chromatography. Vitamin $B_{12}c$ can be distinguished from the other factors by its characteristic absorption spectrum and partition behaviour. The absorption spectrum of vitamin $B_{12}d$ is identical with that of vitamin $B_{12}b$, but they can be separated chromatographically. In addition, vitamins $B_{12}c$ and $B_{12}d$ behave differently from the other factors in the microbiological plate assay technique; they tend to give fuzzy rings of bacterial growth, whereas vitamins B_{12} and $B_{12}b$ give sharp clear-cut rings.

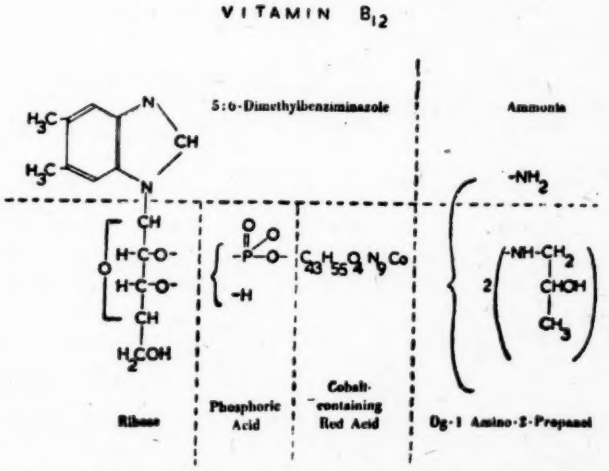
An American team has shown that vitamin $B_{12}b$ is probably identical with vitamin $B_{12}a$, the reduction product of vitamin B_{12} (Brockman *et al.*, 1950). We have confirmed this observation (Anslow *et al.*, 1950). Thus it seems that the new factors are not conjugates of vitamin B_{12} with peptides (like the folic-acid conjugates), but represent slight chemical modifications of the vitamin B_{12} molecule.

Recent simultaneous publications from the Organon and Merck Laboratories describe a surprising new feature of the vitamin B_{12} molecule. It contains a cyanide group co-ordinated with the cobalt atom. Vitamin $B_{12}b$ differs only in the absence of this cyanide group, and is readily converted into vitamin B_{12} by treatment with potassium cyanide (Veer *et al.*, 1950; Brink *et al.*, 1950b; and Kaczka *et al.*, 1950).

Further progress has been made in elucidating the chemical structures of vitamins B_{12} and $B_{12}c$ (see Buchanan *et al.*, 1950a, 1950b; Brink *et al.*, 1950a; Wolf *et al.*, 1950; Chargaff *et al.*, 1950). It is now possible to write a partial formula for vitamin B_{12}.

The latest advance was made by Todd and his colleagues at Cambridge; they isolated intact a large portion of the molecule comprising 5:6-dimethylbenziminazole in glycoside linkage with a molecule of ribose phosphorylated at C_2 or C_3. The cobalt-containing moiety is attached to this phosphorus atom; it represents about two-thirds of the molecule, and its structure has not yet been elucidated. In addition, ammonia and two molecules of D,-1-amino-2-propanol are attached somewhere.

Further light has been thrown on the problem of Castle's intrinsic and extrinsic factors. There is now little doubt that the extrinsic factor is simply vitamin B_{12} itself. When administered orally to cases of pernicious anaemia the pure vitamin is ineffective, except in enormous doses, but it is strongly potentiated by normal



gastric juice (Berk *et al.*, 1948; Bethell *et al.*, 1949; Hall *et al.*, 1949; Campbell *et al.*, 1949). Ungley (1950) and Ternberg and Eakin (1949) have shown that vitamin B_{12} combines with a factor in normal gastric juice—presumably the intrinsic factor—to yield a complex which is microbiologically inactive and non-dialysable. On autoclaving the complex is split, to yield a dialysable active substance, presumably regenerated vitamin B_{12}. These findings have been confirmed by Shaw (1950).

Activities of Vitamin B_{12}

There are indications that vitamin B_{12} has a number of functions in living organisms. A growth-promoting action has been clearly demonstrated in pigs, chicks, and turkeys. There is also a suggestion that vitamin B_{12} may in some instances augment the growth of backward children (Wetzel *et al.*, 1949). It has been shown that vitamin B_{12} is concerned in transmethylation reactions. Thus chicks on a deficient diet can utilize

homocystine as an alternative to methionine only when vitamin B_{12} is given (Jukes, Stokstad, and Broquist, 1950; see also Schaefer *et al.*, 1950). Dubnoff (1950) has shown that vitamin B_{12} augments the reduction of S-S compounds in liver slices.

Jukes, Broquist, and Stokstad (1950) have put forward an ingenious scheme relating the activities in bacterial metabolism of vitamin B_{12}, certain deoxyribosides, folic acid, and "citrovorum factor" ("folinic acid"; see Bardos *et al.*, 1949).

Traina (1950a, 1950b) found that vitamin B_{12} has an antihistamine and anti-anaphylactic effect, but we have failed to confirm the former (Sharpe, Woollett, and Cuthbertson, 1950).

Swendseid *et al.* (1947) showed that liver extract diminishes the excessive urinary excretion of phenols which occurs in pernicious anaemia. Abbott and James (1950) have confirmed this phenomenon with crystalline vitamin B_{12}. This may be connected with the suggested toxic factor of pernicious anaemia, production of which ceases on administration of vitamin B_{12}. In due time these observations will doubtless be welded together into a coherent theory of the mode of action of vitamin B_{12}, but as yet they provide little clue to the mechanism of its haemopoietic activity, beyond its suggested function in the building of nucleic acids.

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EFFECT OF VITAMIN $B_{12}c$ IN PERNICIOUS ANAEMIA AND SUBACUTE COMBINED DEGENERATION OF THE CORD

BY

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The isolation in crystalline form of several factors related to vitamin B_{12} is discussed by Lester Smith in the preceding paper, and differences between vitamin B_{12}, $B_{12}b$, $B_{12}c$, and $B_{12}d$ are defined. The work has a significant bearing upon the treatment of pernicious anaemia, if only because the widely used vitamin B_{12} concentrates derived from bacterial cultures may contain more than one member of this group of red pigments. In the case of vitamin B_{12} itself, quantitative methods have already been applied to dose-response relationships and to its effects in subacute combined degeneration of the cord. Here similar methods are applied to one of the new compounds with the object of determining its activity relative to vitamin B_{12}.

Methods

The methods adopted were those used for the study of vitamin B_{12} (Ungley, 1949a, 1949b). Vitamin $B_{12}c$ was given intramuscularly as a single dose. Doses were graded logarithmically—10, 20, 40, 80, and 160 μg. Doses smaller than 10 μg. were not used, because in tests with vitamin B_{12} they had given less predictable responses than larger doses. Four of the patients had a second test, making 28 tests in all. Conditions governing the inclusion of responses in patients who had received a small transfusion or who had relapsed after

TABLE I.—*Initial Responses to Vitamin $B_{12}c$*

Case No.	Dosage in μg.	Retic. Response %	Red Blood Cell Counts (Millions/c.mm.) at Days Indicated						
			0	5	10	15	20	25	30
1	10	24·6	1·28	1·67	**2·88**	2·61			
2	10	31·2	1·37	1·47	3·09	**3·51**	2·58		
3	10	P.I.	1·64	1·79	**2·85**	2·38			
4	10	9·6	2·46	2·72	3·53	**3·71**	3·63		
2a	10	P.I.	2·58	2·97	3·30	**4·11**	3·89		
1a	10	,,	2·61	2·57	**3·74**	3·71			
5	20	24·8	1·38	1·58	2·74	2·58	3·39	**3·48**	**3·48**
6	20	20·6	1·49	1·95	2·56	2·62	2·60	**3·23**	2·96
7	20	24·6	1·54	1·81	3·11	**3·58**	3·34		
8	20	23·2	1·75	1·96	2·54	2·96	**3·61**		
9	20	7·0	2·48	2·64	3·97	**4·54**	4·06		
10	40	19·6	1·29	1·63	2·43	**3·08**	2·89		
11	40	29·2	1·58	1·71	3·02	3·25	**3·44**	3·29	
12	40	24·8	2·13	2·26	3·11	3·75	**3·80**	3·64	
13	40	12·0	2·19	2·23	2·81	3·66	**3·84**	3·61	
10a	40	P.I.	2·89	4·09	3·99	**4·11**	4·08		
14	80	P.T.	0·94	1·09	3·07	2·97	**3·19**	2·87	
15	80	P.I. / P.T.	1·07	1·15	2·75	**3·20**	3·17		
16	80	24·8	1·24	1·58	2·90	3·27	3·47	**4·24**	3·99
17	80	26·0	1·27	1·46	**2·84**	2·68			
18	80	28·6	1·29	1·52	3·10	3·75	**4·48**	4·25	
19	80	16·6	1·79	1·96	3·01	**3·90**	3·76		
20	80	12·4	2·75	2·99	3·62	**3·83**			
21	160	P.T.	1·38	1·52	2·43	2·85	**2·87**		
22	160	31·2	1·42	2·19	3·02	4·08	4·45	4·82	**5·10**
23	160	27·4	1·70	1·54	3·10	3·53	**3·98**	3·84	
24	160	20·0	1·84	2·42	3·52	3·63	**3·88**	3·46	
21a	160	P.I.	2·87	—	—	4·87	**5·05**		

The highest count is in bold figures. P.I. = previous injection followed by relapse after period without treatment. P.T. = small transfusion before treatment.

Three counts were made a day before or after the day indicated; none of these was a 15-day count.

a previous injection were as described for trials with vitamin B_{12} (Ungley, 1949a).

Treatment was continued until complete remission was attained. Thereafter maintenance requirements were studied as for vitamin B_{12}. Twenty patients who had little or no neurological involvement were given maintenance doses of 10 μg. every two weeks. The adequacy of these low maintenance doses was checked by frequent clinical and haematological observations.

The efficacy of vitamin $B_{12}c$ against the neurological manifestations of pernicious anaemia was observed in 14 patients, including six with subacute combined degeneration of the cord. In two of the latter a quantitative method of assessment was employed (Ungley, 1949b).

Results

A summary of 28 responses observed in 24 patients is given in Table I. There were no unpleasant side-effects in this series.

Reticulocytes

Reticulocytes usually began to rise on the second or third day, reaching a peak on the fifth or occasionally on the sixth or seventh day. There was no significant correlation between dosage (in the range 10 to 160 μg.) and the day of onset, day of peak, or height of peak of the reticulocyte response. In Fig. 1 the responses are compared with the standard of Isaacs and Friedman (1938). They are not significantly worse or better than those obtained with similar doses of vitamin B_{12}. Reticulocyte responses were valuable for following progress in the early stages of treatment, but the height of the peak was not a satisfactory guide to the rate at which the anaemia would subsequently improve.

Increase of Red Blood Cells

A better criterion of response was the increase of red blood cells in 15 days. In Fig. 2 the actual increases are plotted against the initial red blood cell levels. Lines showing the expected response to graded doses of vitamin B_{12} (Ungley, 1949a) are included for comparison. As with vitamin B_{12}, there were wide individual variations in the response to a given dose.

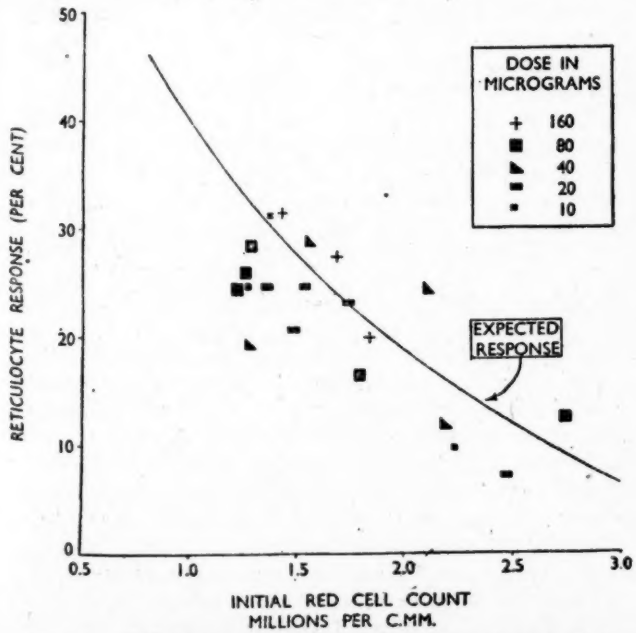

FIG. 1.—Reticulocyte responses (peak) of 20 patients to their first injection of vitamin $B_{12}c$, compared with the expected response to liver extract calculated from the formula of Isaacs and Friedman (1938).

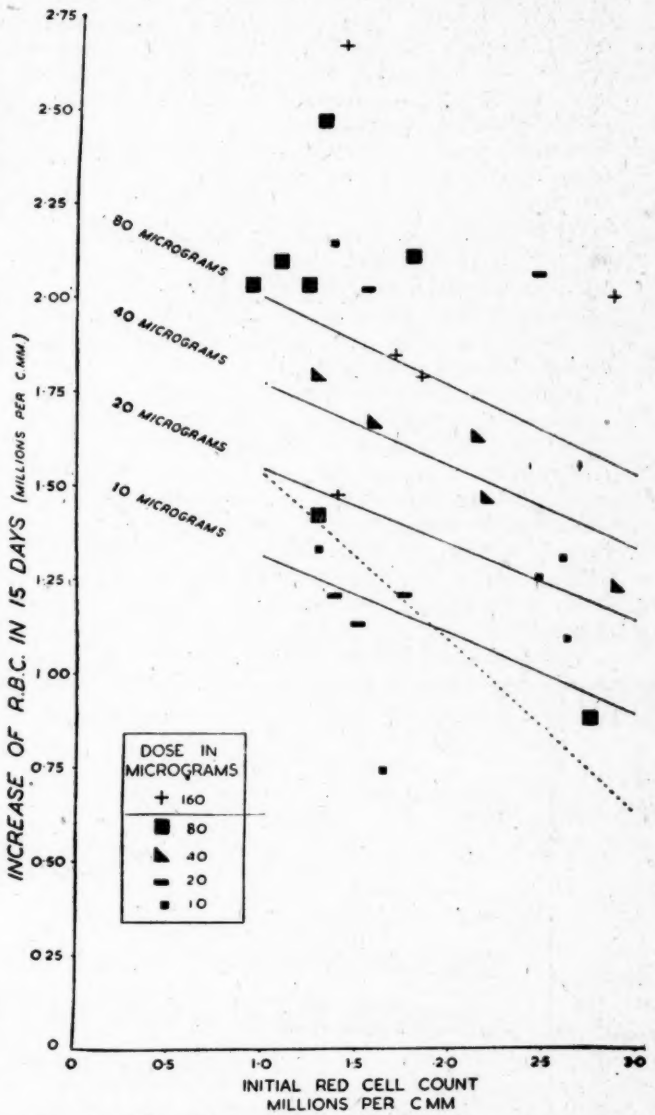

FIG. 2.—Observed increase of red blood cells in 15 days in 28 instances after a single injection of vitamin $B_{12}c$. The lines indicate the expected response from equal doses of vitamin B_{12} (Ungley, 1949a). The dotted line corresponds to the formula of Della Vida and Dyke (1942) for "average" responses to liver extract.

In Table II and Fig. 3 the observed mean responses to vitamin $B_{12}c$ are compared with the expected response from a similar dose of vitamin B_{12} according to the formula. It was estimated previously that the standard deviation of an actual increase from the expected would be about $\pm$330,000 red blood cells per c.mm. The

TABLE II.—*Mean Increase of Red Blood Cells After Graded Doses of Vitamin $B_{12}c$ Compared with the Expected Response to Equal Doses of Vitamin B_{12}*

Dose in μg.	No. of Cases	Mean Initial R.B.C.	Mean Actual Increase	Mean Expected Increase	Mean Differences	Standard Error of Differences $= \frac{0.33}{\sqrt{N}}$
		Millions per c.mm.				
10	6	1·99	1·35	1·12	+0·23	±0·14
20	5	1·73	1·52	1·39	+0·13	±0·15
40	5	2·02	1·55	1·54	+0·01	±0·15
80	7	1·48	1·86	1·88	−0·02	±0·12
160	5	1·84	1·95	2·00	−0·05	±0·15
Total	28	1·81	1·65	1·59	+0·06	±0·06

standard error for the average of a group of patients would, however, be less than this. It will be noted that in only one group (10 μg.) does the average difference between the observed and expected increases exceed the standard error.

By this criterion, therefore, there is no detectable difference between the haemopoietic effects of vitamin B_{12} and $B_{12}c$.

When all 28 responses are considered together even more valid comparisons become possible. It will be seen that the mean response to vitamin $B_{12}c$ was almost identical with the response expected from equal doses of vitamin B_{12}. The average difference is +0.06—that is, +60,000 cells per c.mm.

Table II and Fig. 3 show a tendency for patients treated with smaller doses of vitamin $B_{12}c$—that is, 10 or 20 μg.—to respond better than would be expected. Although the mean differences do not exceed twice the standard error, either individually or collectively, they do, however, suggest that the log. dose-response curve may be a little less steep than was originally thought. The difference is not likely to be very significant, and many more observations would be needed to establish it conclusively.

The greater consistency of responses to 40 μg. and over suggests that doses of this order would be more valuable than smaller doses in future therapeutic trials.

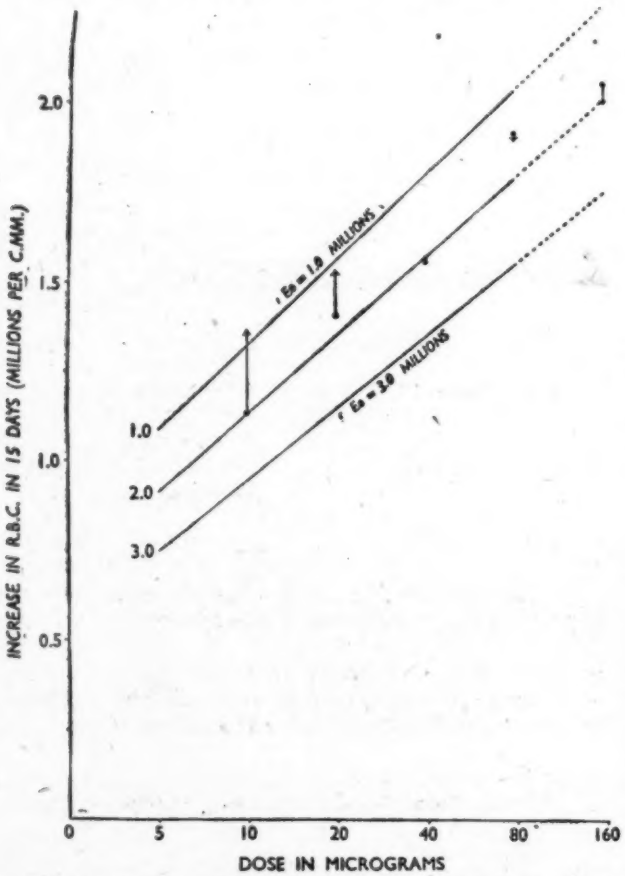

FIG. 3.—The mean difference between observed increase of red blood cells in 15 days after graded doses of vitamin $B_{12}c$ and the response expected from equal doses of vitamin B_{12}. The differences have been superimposed on the dose-response curve to graded doses of vitamin B_{12} (spaced logarithmically). The difference between observed means and expected increase is shown by vertical lines. Dot = initial count; length of line = deviation from expected response; arrow shows whether the deviation is above or below expectation. The differences were in each case less than twice the standard error of the means (see Table II).

The mean red blood cell counts at 0, 5, 10, and 15 days are shown in Table III. The *duration* of the increase of red blood cells (evident from the bold figures in Table I) was not of much value for the purpose of measuring the relation between dosage and response.

TABLE III.—*Mean Red Blood Cell Counts During the First 20 Days of Treatment*

Dose in μg.	No. of Cases	Mean Red Blood Cell Counts				Cases Followed 20 Days		
		0 Day	5 Days	10 Days	15 Days	No.	R.B.C.	
							0 Day	20 Days
10	6	1·99	2·20	3·23	3·34	3	2·14	3·37
20	5	1·73	1·99	2·98	3·25	5	1·73	3·40
40	5	2·02	2·38	3·07	3·57	5	2·02	3·61
80	7	1·48	1·68	3·04	3·34	5	1·27	3·61
160	5	1·84	2·18	3·28	3·79	5	1·84	4·01

Total Dosage to Complete Remission

Some observers have attempted to calculate requirements for vitamin B_{12} by noting the total amount given before remission was attained and dividing by the number of days since treatment began. The answers obtained vary widely according to the size and spacing of the doses, and do not provide information suitable for calculating requirements for vitamin B_{12} or $B_{12}c$.

Other Findings

The usual improvement in appetite and well-being, relief of sore tongue and gastro-intestinal symptoms, and gain in weight were observed as after vitamin B_{12} itself. Neurological manifestations are discussed separately. Sixty-seven white blood cell counts in 24 patients before treatment ranged from 2,000 to 10,400 per c.mm. —mean 4,300. When remission was attained (red blood cells over 4,500,000 per c.mm.) 108 white blood cell counts ranged from 3,500 to 10,300 per c.mm. (mean 6,650).

Maintenance

The maintenance period was arbitrarily fixed as beginning when red blood cells first reached or exceeded 4,500,000, or as soon after that as regular maintenance doses were begun. Twenty patients received maintenance doses of 10 μg. every two weeks for four to nine months. Only eight of them have been on maintenance therapy more than six months.

One woman was given iron for a time because her haemoglobin values were slightly below average (lowest 12.1 g. per 100 ml.). Normality was restored. Another woman, not of child-bearing age, often had haemoglobin values of 12 g. or even less, but in her case the red cell counts were often slightly subnormal too (lowest count 4,300,000). Mean corpuscular volume (M.C.V.) ranged from 80.3 to 96.5 μ^3 (mean 85.4). She felt well and had no complaints. Without any increase in dose the counts rose to 5,000,000 or over and remained there. In the other 18 patients very few red blood cell and haemoglobin values fell outside the accepted normal range, and none remained persistently abnormal.

Taking all 20 patients together, individual red blood cell counts ranged from 4,310,000 to 5,610,000 per c.mm. Mean counts ranged from 4,610,000 to 5,260,000. The mean of the means was 5,040,000 per c.mm.

Individual haemoglobin values ranged from 11.3 to 15.7 g. per 100 ml. Mean values ranged from 12 to 14.8 (mean of all means, 13.9 g. per 100 ml.).

Mean values for M.C.V. in all 20 cases ranged from 80.1 to 94.5 μ^3 (mean 87.1). One patient whose red

blood cell and haemoglobin values were always normal (means 5,160,000 and 14.8 g.) had a slightly increased M.C.V. (96–99.2 μ^3) on 5 out of 11 occasions. The mean of the 11 readings was 93.2 μ^3. The patient felt well and had no symptoms. In the remaining 19 patients M.C.V. values of this order (96–98 μ^3) were encountered only seven times in 142 tests.

Mean values for mean corpuscular haemoglobin concentration (M.C.H.C.) for all cases ranged from 30.1 to 35.1% (mean 31.8%)

In none of the 20 cases was it necessary to increase the maintenance dose. It must be emphasized, however, that the patients were seen every two to four weeks and were told to report immediately if unwell, and that patients with more than slight neurological involvement were not given this low dosage. In routine cases seen at infrequent intervals we normally advise much larger doses—at least 60 μg. (of vitamin B_{12} concentrate) every three weeks—with instructions to increase the dosage if intercurrent infection supervenes.

Neurological Manifestations

The effects of vitamin $B_{12}c$ on the neurological manifestations of pernicious anaemia have been observed in six patients with subacute combined degeneration of the cord, of whom two have been studied quantitatively. To facilitate comparison between these two cases and patients treated with liver extract or vitamin B_{12} (Ungley, 1949b) the neurological changes in the first six months of treatment are analysed. The rate of reduction in scores for individual symptoms and signs and in the total score is shown in Figs. 4 and 5.

Case A

A woman aged 39 had numbness of the fingers for 10 months; numbness, weakness, and tightness in the legs for seven months; and considerable difficulty in walking for two months. The tongue had been sore and was unduly clean and red. There was never much anaemia, the lowest red blood cell count being 3,120,000 per c.mm., haemoglobin 9.3 g. per 100 ml., P.C.V. 30%, M.C.V. 96.2 μ^3, M.C.H. 30.1 $\mu\mu$g., M.C.H.C. 31%. Marrow puncture showed early megaloblastic change. Plasma bilirubin was 0.8 mg. per 100 ml. (direct reaction negative). There was achlorhydria even after histamine and alcohol. The blood Wassermann reaction was negative.

Vitamin $B_{12}c$ was given in doses of 40 μg. a week for six months and every two weeks since—10 months in all. The blood count was restored to normal within a month.

Initially the patient took only a few steps alone, otherwise holding lightly to the furniture. The gait was ataxic, and she could not keep to a test line 7.5 cm. broad. She staggered severely when turning. After six months she was still not quite as steady as before her illness and could not run, but she could walk a mile or more without help. Gait was normal on the 7.5-cm. line. In Romberg's test she overbalanced at once. Normality was restored within four months. Numbness in the fingers disappeared completely. Paraesthesiae in the lower limbs receded from the groins and buttocks to below the knees.

In tests for co-ordination the heel usually missed the toe by 5 to 7 cm. In the sliding test the heel wavered unevenly down the shin or slid off. The mean error in 10 attempts to locate spots on the leg with the opposite heel was 6 to 7 cm. In six months almost complete normality was restored. The heel–knee–toe and sliding tests were normal eight times and almost normal twice in 10 attempts at each. The mean error in the location test was 1 to 2 cm.

There was little improvement in joint sense in the toes. Vibration sense remained absent in all 10 test areas. The recognition of figures written on the soles remained somewhat defective. Knee- and ankle-jerks were grossly exaggerated and patellar and ankle clonus were elicited. Normality was restored in six months. Both plantar responses were clearly extensor. After three months the left plantar response was always flexor. The right one also became flexor, but never so clear-cut as the left.

In six months the total score fell from 70.5 to 27—a reduction of 62%, compared with the expected 53% (Ungley, 1949b).

After 10 months the improvement was maintained. She walked quite normally and could even run a little. Numbness was confined to the great toes.

Case B

A woman aged 52 had paraesthesiae for one year, and unsteadiness in walking and dysuria for four months. She fell frequently and could not stand with her eyes closed.

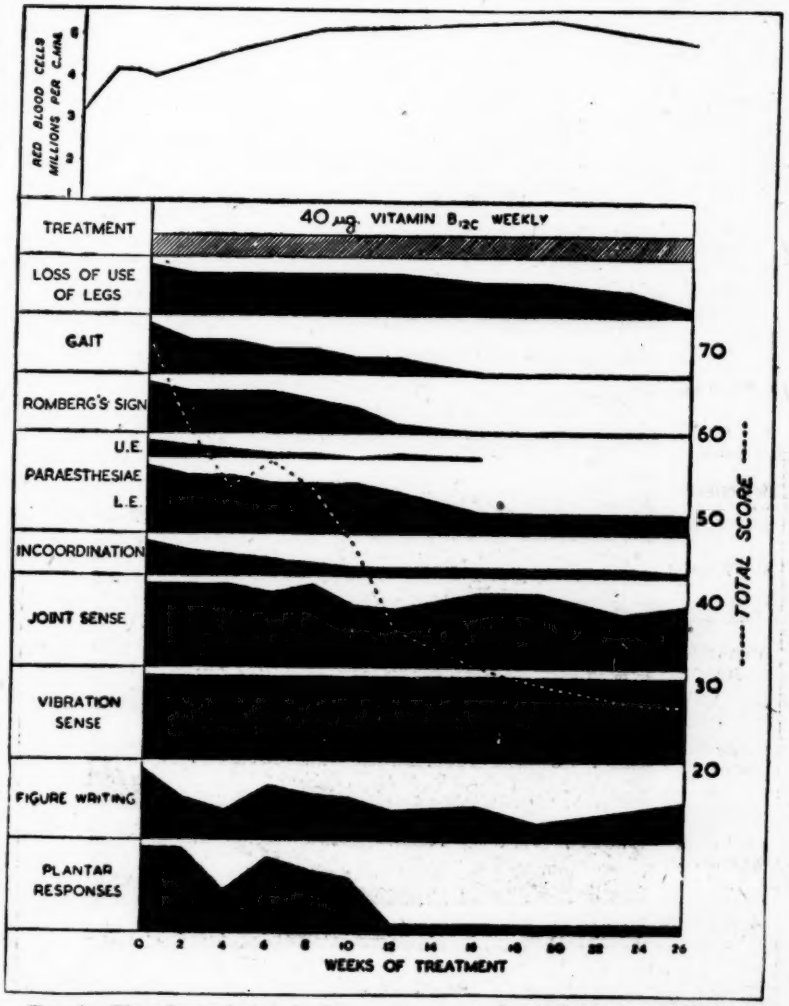

FIG. 4.—The effect of vitamin $B_{12}c$ on the scores for individual symptoms and signs during the first six months of treatment in Case A. The dotted line indicates changes in the total score for neurological defect—that is, the sum of the scores for symptoms and signs. U.E. = Upper extremities; L.E. = Lower extremities.

Her diet had been poor. In an average week she ate one egg, meat once, fish once, potatoes twice, and cabbage perhaps once. Fresh fruit was consumed perhaps once a month. She ate more than her ration of butter, but drank milk only in tea.

Her mouth had been ulcerated and the tongue was unduly clean. Blood pressure was 198 systolic, 100 diastolic. There was achlorhydria even after histamine and alcohol. The blood Wassermann reaction was negative. The marrow was megaloblastic. Plasma bilirubin was 0.8 mg. per 100 ml. (direct reaction negative). Red blood cells numbered 2,750,000 per c.mm., haemoglobin 10.5 g. per 100 ml., reticulocytes 0.4%, P.C.V. 33%, M.C.V. 120 μ^3, M.C.H. 38.5 $\mu\mu$g., M.C.H.C. 31.8%, white blood cells 2,800.

After a single injection of 80 μg. of vitamin $B_{12}c$ reticulocytes rose to 12.4% on the fifth day and red blood cells increased to 3,630,000 per c.mm. in 15 days.

Thereafter she received 40 μg. a week. After five weeks red blood cells numbered only 4,200,000 per c.mm. and haemoglobin 11.8 g. per 100 ml., so the dose was increased to 80 μg. a week. At 10 weeks haemoglobin had fallen to 10.1 g. per 100 ml. following severe menstrual loss, and iron was given. At 21 weeks normal blood values had been restored and iron was discontinued. At six months red blood cells numbered 5,210,000 per c.mm., haemoglobin 13.6 g. per 100 ml., P.C.V. 44%, M.C.V. 84.6 μ^3, M.C.H. 26 $\mu\mu$g., M.C.H.C. 30.9%, white blood cells 2,800 per c.mm. The dosage of vitamin $B_{12}c$ was then reduced to 80 μg. every two weeks. At nine months the haematological findings, including absolute values, were still within normal limits.

Initially she could walk 15 yards alone, staggering on a base 30 to 40 cm. wide. After six months she walked a mile, most of it without assistance; she could step along the 7.5-cm. test line, making seven mistakes in 25 yards. She had sometimes fallen while attempting to wash her face, and in Romberg's test she overbalanced at once. After six months she was steady while washing; in Romberg's test there was some sway, but she did not usually overbalance.

She had frequency, urgency, and sometimes difficulty in starting micturition. After six months she still had some urgency. Paraesthesiae in the hands became slight and infrequent. Severe paraesthesiae extending to the groins receded to the soles and toes.

In tests for co-ordination the heel missed the toe by an average of nearly 10 cm., the heel slid off the shin on to the bed once or twice at each attempt, and efforts to locate spots on the leg with the contralateral heel missed by an average of 8 cm. Six months later the toe was missed by an average of 1.5 cm. The mean error in location was 2 cm., and the sliding test was usually performed with only a slight waver.

There was no return of joint sense in the toes, and vibration sense remained absent in all 10 test areas. Recognition of figures written on the soles was not improved. Excessive adductor tone in the lower limbs became normal. Exaggerated ankle-jerks became normal and ankle clonus disappeared, but knee-jerks remained rather active and extensor plantar responses were unchanged.

In six months the total score decreased from 78 to 53—a reduction of 32%, compared with the "expected" reduction of 53%.

After nine months she was even less ataxic and could walk a mile alone. In Romberg's test there was only slight sway. Paraesthesiae extended to the ankles.

Comment.—One expects wide individual variations in the response to treatment, and it is not surprising that one patient had more and one less than the expected reduction in total score. The mean reduction for the two cases was 47%, compared with the expected 53% for patients with difficulty in walking of similar duration. Many more cases would be needed to determine whether vitamin B_{12} and $B_{12}c$ are equally effective on a dose-for-dose basis.

The third case is mentioned only in parenthesis, for the patient was too ill for a controlled trial: treatment with vitamin $B_{12}c$ had to be supplemented by physiotherapy, a high protein diet, and extra vitamins.

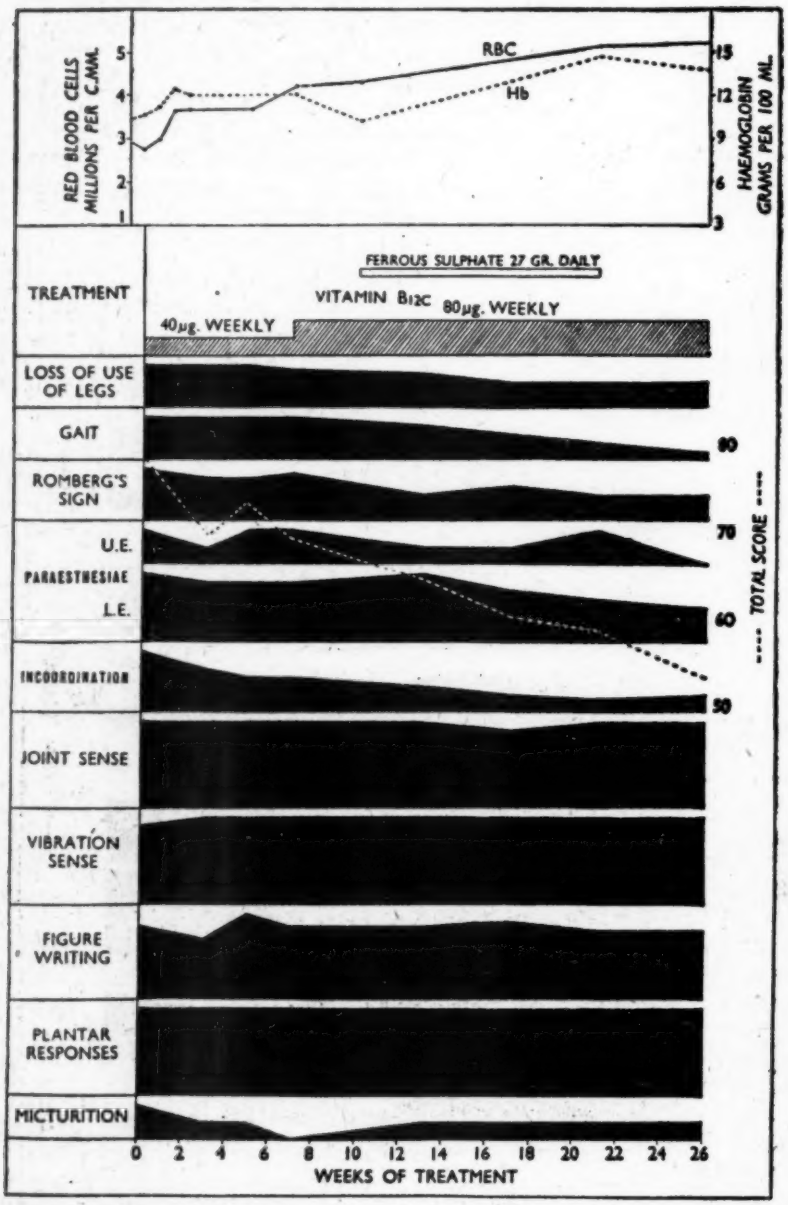

FIG. 5.—Changes in the scores for neurological symptoms and signs during the first six months of treatment in Case B. Dotted line = changes in total score.

Case C

A woman aged 51 had symptoms referable to pernicious anaemia for three years and a staggering gait for nine weeks. She rapidly developed paraplegia in flexion, with flexor spasms, incontinence of urine and faeces, urinary and pulmonary infections, and deep decubitus ulcers. The blood picture was that of pernicious anaemia, with red blood cells numbering 2,500,000 per c.mm. The marrow was megaloblastic. After an initial dose of 80 μg. of vitamin $B_{12}c$, reticulocytes rose to 15.6% on the fifth day and in 10 days the red blood cells numbered 3,470,000 per c.mm.

Because of complications the dosage of vitamin $B_{12}c$ was then stepped up to 20, 40, and finally to 80 μg. daily and supplemented by transfusions, a high-protein diet, vitamins A, C, and D, thiamin, riboflavin, nicotinamide, and folic acid.*

The urinary infection was brought under control by sulphonamides, antibiotics, and tidal drainage. Physiotherapy helped to relieve flexor spasms and contractures. Decubitus ulcers healed only when the patient was nursed on her face. After 10 months she walked with a stick and for short distances alone. There was no incontinence of urine, but control of micturition and defaecation was not yet normal.

Comment.—Complicating infections and the need for multiple remedies prevented quantitative evaluation of the response to vitamin $B_{12}c$, but the case is worth mentioning because the outlook seemed so bad and the recovery was so remarkable.

Other Cases

The progress of three other patients with subacute combined degeneration of the cord was followed. One improved and one remained unchanged while receiving 40 μg. of vitamin $B_{12}c$ per week. The third showed rapid improvement after two doses of 160 μg. and continued to improve on the low maintenance dose of 10 μg. every two weeks.

Eight patients had paraesthesiae without definite signs of subacute combined degeneration of the cord. In one of these, paraesthesiae disappeared after 40 μg. a week for six weeks followed by 10 μg. every two weeks for five months. In another, tingling in the feet persisted despite the injection of 80 μg. every three weeks. The remaining six received only 10 μg. every two weeks: in four the paraesthesiae disappeared and in two they improved.

Considered as a whole the findings suggest that vitamin $B_{12}c$, like liver extract or vitamin B_{12}, is capable of arresting the nervous lesions of pernicious anaemia.

Summary

The therapeutic value of vitamin $B_{12}c$ in pernicious anaemia was assessed and compared with that of vitamin B_{12}.

Twenty-eight responses to single doses were observed in 24 patients. Doses were graded logarithmically—10, 20, 40, 80, and 160 μg. The increase of red blood cells in 15 days after a given dose showed the usual individual variations, but the mean of 28 responses was almost identical with the response expected from equal doses of vitamin B_{12}. The log. dose-response curve did not differ significantly from that of vitamin B_{12}. The greater consistency in response to doses of 40 μg. and over suggests that such doses would be more useful than smaller doses in future therapeutic trials.

Twenty patients with little or no neurological involvement have been maintained for four to nine months on doses of 10 μg. every two weeks. Red blood cell or haemoglobin values were temporarily slightly subnormal in two patients: in one normality was restored with iron, and in the other without alteration of treatment. A third patient had a slightly raised M.C.V. None of the 20 patients showed neurological, lingual, alimentary, or other symptoms of relapse. These results are as good, so far, as those observed with similar maintenance doses of vitamin B_{12}. Such low maintenance would be dangerous, however, in patients not under close observation. For routine purposes we normally give at least 60 μg. every three weeks—more if there is neurological involvement or intercurrent infection.

The efficacy of vitamin $B_{12}c$ against the nervous disorders of pernicious anaemia was tested in six patients with subacute combined degeneration of the cord, two of whom were subjected to quantitative studies, and in eight patients with minor neurological involvement. None of the patients became worse and all except two were improved.

This experiment has failed to show any difference between vitamins $B_{12}c$ and B_{12}, but even a difference of 30% in haemopoietic potency would result in only a difference of about 5% in the average response of 28 cases: a large difference in dosage causes only a small increase in response. Later analyses based on increases of haemoglobin and of packed cell volume in 15 days also failed to demonstrate any difference in potency between the two vitamins. Although similar limitations apply to these results they greatly strengthen the conclusions based on increase of red blood cells alone. Both vitamins are effective against the neurological manifestations of the disease.

*It was considered safe to give folic acid because the supply of vitamin B_{12} was adequate.

I am grateful to the medical, nursing, clerical, and laboratory staff of the hospital and to many general practitioners for their co-operation. I am also indebted to Dr. E. Lester Smith and his colleagues of the Research and Development Division, Glaxo Laboratories, Ltd., Greenford, who prepared and supplied the crystalline vitamin $B_{12}c$ used in these investigations.

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The thirty-first annual report (1949–50) of the Walter and Eliza Hall Institute in Melbourne shows a scientific staff of 24 under the directorship of Sir Frank Burnet, F.R.S. The clinical research unit, containing nearly half the staff, has been at work on glucose-tolerance curves after gastrectomy, gastric biopsy in pernicious anaemia, digestion and absorption after massive resection of the small intestine, the control of malnutrition, and similar problems. The virus research, for which the institute is noted, has been mainly following up the discovery that influenza virus appears to contain an enzyme (receptor-destroying enzyme, or R.D.E.), which attacks the surface of the red cell, and also various mucins, which are complex polysaccharides. Because R.D.E. inactivates urinary gonadotrophin both *in vitro* and *in vivo*, it was given intravenously in large doses to mice, and in one group a definite though temporary suppression of conception was obtained. This opens up interesting possibilities in the control of reproductive function. In order to further immunological studies of human influenza the epidemiological unit of the Eliza Hall Institute has established what are called "listening posts" among groups of the population, so that the beginning of an epidemic can be readily detected. Taking part in this scheme are two public schools, two hospitals, a naval depot, and a babies' home. Altogether about 3,000 individuals are under survey. During 1950 influenza occurred in the babies' home, affecting both staff and children. Those recently arrived from Northern Europe were most prone to the infection. Few of the Australian staff developed the disease.

VITAMIN B_{12} AND FOLIC ACID IN MEGALOBLASTIC ANAEMIA AFTER TOTAL GASTRECTOMY

BY

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Macrocytic anaemia following total gastrectomy has been described on a number of occasions. Many of the cases reported have, however, been inadequately studied; in particular, little attention has been paid to the possibility of dietary deficiency following operation, and special investigations such as reticulocyte counts and bone-marrow examinations have been few. There is no clear conception of the relationship of the anaemia to Addisonian pernicious anaemia. Wintrobe (1946) stated that "at least 10 acceptable cases with the typical blood picture of pernicious anaemia have been reported to date, and there is an equal number or more whose histories as recorded are less satisfactory." In the last four years at least six more cases have been published (Weir, 1946; Bethell, Meyers, Andrews, Swendseid, Bird, and Brown, 1947; Morgans, Rimington, and Whittaker, 1947; MacDonald, Ingelfinger, and Belding, 1947; Beebe and Meneely, 1949), but the haematological details are scanty.

Treatment with liver extracts has, in general, proved satisfactory. Folic acid has also been used with success (Morgans, Rimington, and Whittaker, 1947).

The present case of megaloblastic anaemia following total gastrectomy is reported because of its rarity and theoretical interest. The operation was performed for gastric contraction after acute corrosive poisoning. So far as is known this is the first recorded case of its kind to be treated with vitamin B_{12}.

Case Report

The patient, a labourer aged 47, drank, in mistake for cold tea, one-third of a cupful of solder "flux" on the evening of July 31, 1944. The "flux" consisted of zinc chloride 66%, acetic acid (90% glacial) 1%, and distilled water 33%. Immediately afterwards he felt sick but experienced no pain. He at once drank a strong solution of salt in water and began to vomit; the vomitus was at first watery but soon became blood-stained and very dark. An hour later gastric lavage was performed by his doctor, using a warm solution of sodium bicarbonate. Vomiting continued throughout the night, and he was admitted to the Western Infirmary, Glasgow, on August 1 in a state of shock. Acute phlegmonous gastritis developed, and by the end of August there was clinical and radiological evidence of gastric contraction. Jejunostomy was performed by Mr. A. W. Kay on September 10. His weight before operation was 105 lb. (47.62 kg.). In the next six weeks several attempts at oral feeding had to be abandoned because of vomiting. His weight fell gradually, and on October 8 radiological examination confirmed that gastric contraction was increasing.

Professor C. F. W. Illingworth performed a total gastrectomy on October 28. About 1 in. (2.5 cm.) of the duodenum and a small portion of the oesophagus were removed with the stomach, which was small, thick-walled, and extensively scarred; the lower end of the oesophagus was anastomosed to the jejunum. His weight before operation was 98 lb. (44.45 kg.). The post-operative course was uneventful, and in two weeks he could eat small quantities of solid food without discomfort or vomiting. He was discharged on November 21, when his weight was 100 lb. (45.36 kg.).

Subsequent Course

The patient reported at the follow-up clinic at regular intervals until the end of 1947. During 1948 and 1949 he failed to attend, but reappeared in June, 1950. Blood findings are shown in detail in Table I.

March, 1945.—Weight 118 lb. (53.52 kg.); appetite good, and able to eat an average meal; a feeling of emptiness between meals; no pain or vomiting; returned to work in January, 1945.

October, 1945.—Weight 121 lb. (54.88 kg.); symptom-free and taking normal meals; colour good; *x*-ray examination showed the barium passing direct into the jejunum, which dilated as it passed through.

TABLE I.—*Haematological Details*

Date	Hb (g.%)	P.C.V. (%)	R.B.C. (mill. per c.mm.)	M.C.V. (μ^3)	M.C.H.C. (%)	M.C.D. (μ)	W.B.C. per c.mm.	Icterus Index	Bone Marrow	Treatment* (μg. Vitamin B_{12})	Remarks
16/10/44	12·0	—	4·60	—	—	—	—	—			
13/11/44	16·0	52	5·40	96	31	—	10,400	—	Normal		Total gastrectomy on 28/10/44. Six pints of blood transfused
6/10/46	12·3	40	3·51	113	31	—	8,400	—	Normoblastic but premature haemoglobinization of normoblasts		Liver therapy prescribed, but not more than 5 injections given during 1946–7
15/6/50	4·9	14	0·95	147	35	9·0	2,400	5	Megaloblastic	40	Blood film typical of Addisonian pernicious anaemia
22/6/50	6·2	22	1·39	158	28	9·0	3,100	5			
30/6/50	7·1	24	1·70	141	30	8·4	3,300	3		20	
5/7/50	8·4	30	2·30	130	28	8·4	—	—		20	
14/7/50	9·4	34	3·31	103	28	8·2	—	—		20	
21/7/50	10·4	34	3·62	94	30	8·2	—	—		20	
28/7/50	9·8	33	3·53	94	30	8·2	—	—		40	
4/8/50	10·4	34	3·71	92	29	8·2	5,300	3		40	
11/8/50	10·0	35	3·65	96	29	8·2	5,200	5		40	
18/8/50	10·8	36	3·80	95	30	8·0	—	3	No gross abnormality	40	
26/8/50	10·2	35	3·62	97	29	8·2	—	—		40	
2/9/50	10·3	35	3·75	93	29	8·1	—	3		40 μg. + folic acid 20 mg. daily	
16/9/50	12·2	42	4·60	91	29	8·0	6,400	3		40	

* Treatment was given on dates shown after blood investigations were completed.

April, 1946.—Weight 126 lb. (57.15 kg.); taking ordinary diet without discomfort; no diarrhoea.

October, 1946.—Weight 129 lb. (58.51 kg.); no abnormal symptoms. Routine blood examination (Table I) revealed a slight macrocytic normochromic anaemia. Sternal marrow biopsy showed normoblastic erythropoiesis, but some of the normoblasts were prematurely haemoglobinized. An early stage of a "liver-factor" deficiency anaemia was diagnosed on the strength of the previous history, the macrocytosis and normal M.C.H.C., and the marrow appearances. Liver therapy was prescribed.

September, 1947.—Weight 120 lb. (54.43 kg.); complaint of dizziness immediately after meals, passing off in about 30 minutes. Not more than five liver injections had been given, at very irregular intervals, during the previous year. He was not enthusiastic about the injections, because he felt well without them. Diet consisted mainly of fish, meat, tripe, potatoes, milk puddings, bread, fruit, and milk; total calories about 2,000.

December, 1947.—Weight 116 lb. (52.61 kg.); dizziness immediately after meals persisted. A glucose-tolerance test gave a typical "lag storage" curve. Barium-meal examination showed no evidence of abnormal dilatation of the small bowel.

Recent Illness

The patient reported again in June, 1950, complaining of increasing tiredness and dyspnoea on exertion of six months' duration. His appetite was good, but a few minutes after each meal he suffered from a feeling of distension accompanied by light-headedness and a desire to lie down. These symptoms passed off in half an hour. For a few months he had noticed paraesthesiae of his finger-tips, but his tongue had not been painful. He had received no liver injections since the summer of 1947.

He was readmitted on June 13, having been at work until one week previously. He looked pale and thin, and his weight was 104 lb. (47.17 kg.). His tongue was normal in appearance, and the spleen was not palpable. The nervous system was normal.

Investigations.—Examination of the peripheral blood (Table I) revealed a severe macrocytic normochromic anaemia; the blood film contained macropolycytes and a few late megaloblasts, and appeared typical of Addisonian pernicious anaemia. There was a leucopenia, but the serum bilirubin was not raised. Bone-marrow smears showed megaloblastic erythropoiesis, and giant metamyelocytes were numerous. Barium-meal examination revealed no abnormality of the oesophagus or upper loops of the jejunum. The faeces were normal in appearance and contained no blood; fat comprised 12% (average of three specimens) of the dry substance of the stool. A fat-balance test was not done.

The daily food intake prior to readmission was estimated at 2,100 calories (protein 80 g., fat 85 g., carbohydrate 260 g.). He took three main meals, with milk drinks between; eggs, meat, tripe, fruit, potatoes, and fish were consumed regularly. Vitamins were considered to be adequate. The glucose-tolerance test again gave a "lag storage" curve.

Treatment.—An initial injection of 40 μg. of vitamin B_{12} concentrate (prepared from *Streptomyces griseus*) was given on June 15. Within a few days he began to feel better. The reticulocyte response and rise of red cells in the first 15 days are shown in Table II. Further injections were given as detailed in Table I, and there was marked clinical improvement. The haemoglobin and red blood cells continued to rise for five weeks, but in the next six weeks there was no further increase despite frequent doses. The peak levels for haemoglobin and red blood cells were 10.8 g.% and 3.8 millions per c.mm. respectively. At this stage the bone marrow was considered to be normal, and there was no important degree of iron deficiency. The addition of folic acid (20 mg. a day) then raised the haemoglobin to 12.2 g.% and the red blood cell count to 4.6 millions per c.mm. in two weeks.

TABLE II.—*Rise of Red Blood Cells and Reticulocyte Response in the First 15 Days after a Single Injection of 40 μg. Vitamin B_{12}*

Day of Treatment	Hb (g.%)	R.B.C. (mill. per c.mm.)	Reticulocytes (%)
0	4·9	0·95	0·5
1	—	—	0·5
2	—	—	1·5
3	—	—	1·5
4	—	—	10·0
5	5·3	1·06	27·0
6	—	—	28·0
7	6·2	1·39	27·5
8	—	—	18·5
9	—	—	8·0
10	6·6	1·55	5·0
11	—	—	4·0
12	—	—	1·5
13	—	—	0·5
14	—	—	1·0
15	7·1	1·70	1·0

The patient was discharged from hospital on July 7 and returned to full employment a month later. On September 9 he felt extremely well and weighed 117 lb. (53.07 kg.). It is noteworthy that the "dumping syndrome" ceased when his general condition improved, and there has been no recurrence.

The effect of vitamin B_{12} in maintenance treatment is being studied.

Discussion

It is interesting to consider the pathogenesis of the megaloblastic anaemia which occasionally follows total gastrectomy in the light of the classical theory of erythropoiesis. Meulengracht (1935) showed that, in the hog, the duodenum as well as the pyloric and cardiac regions of the stomach possessed anti-anaemic activity. In human beings, however, Castle, Townsend, and Heath (1930) found that duodenal secretion contained no intrinsic factor, and Fox and Castle (1942) produced strong evidence that only the body of the stomach is important. This is the site which shows diagnostic atrophic changes in patients dying of pernicious anaemia (Magnus and Ungley, 1938). Recently Landboe-Christensen and Plum (1948) have suggested that the pyloric area, in man, is a significant but minor source of intrinsic factor. Patients who have undergone total gastrectomy should therefore, theoretically, develop megaloblastic anaemia when their store of anti-anaemic principle is exhausted. The operation is, however, usually undertaken for malignant disease and the average survival time is short.

In 1929 only 10 cases were known to have lived for a year or longer (Finney and Rienhoff, 1929). This probably explains the clinical fact that macrocytic anaemia is relatively rarely encountered after total gastrectomy. Time is required for its development, and Bethell, Sturgis, Rundles, and Meyers (1945) considered that complete removal of the stomach is invariably followed by macrocytic anaemia provided that the patients live long enough. MacDonald, Ingelfinger, and Belding (1947) collected, from the literature and by correspondence, details of 53 patients who had survived for three or more years after operation. Twelve developed macrocytic anaemia and five anaemia of doubtful nature. Thirty-six did not develop this anaemia up to the time of death or review. Of the last group, seven received prophylactic liver therapy, 19 probably had liver but no accurate information was available, and 10 definitely had no liver. An exceptional case was stated to be alive and well 8½ years after operation even in the absence of prophylactic liver.

The time between operation and the first diagnosis of macrocytic anaemia in the cases previously recorded

varies from five months (Ungley, 1932) to eight years (Dennig, 1929 ; Hochrein, 1929 ; Weir, 1946) ; the average is approximately four and a half years. The case quoted by Hurst (1932) as having developed pernicious anaemia and subacute combined degeneration of the spinal cord 17 years after total gastrectomy was originally reported by Ellis (1925) to have undergone only partial gastrectomy. The length of the average latent period requires consideration, and in this respect the work of Schwartz and Legere (1944) is of interest. These authors found, in a study of 54 cases of Addisonian pernicious anaemia, that relapses occurred 2–38 months after stopping liver therapy. They pointed out that in individual cases the time of relapse was unpredictable and depended, apart from intercurrent disease, on the quantity of anti-anaemic factor stored, the consumption of food factors containing active principle, and the extent of deficiency of the intrinsic factor.

Goldhamer (1937) found that the lack of intrinsic factor in pernicious anaemia is not absolute but differs in degree in different patients. After total gastrectomy the intrinsic factor must, according to accepted theory, be completely absent, and yet the average period between operation and the development of macrocytic anaemia is considerably longer than the longest of the remissions noted by Schwartz and Legere (1944). The surgical patients may start off with a higher store of active principle than is carried by a treated case of pernicious anaemia, but it is difficult to conceive of preformed stores great enough to postpone the development of macrocytic anaemia for eight years. It is likely that other factors are involved, and the upset in vitamin B_{12} metabolism following total gastrectomy may be less serious, at least in the beginning, than in Addisonian pernicious anaemia.

Recently investigations have been made into the presence in the intestinal wall of intrinsic factor as distinct from extrinsic and intrinsic factor together. The existence of intrinsic factor in the duodenal mucosa has been established (Bethell, Swendseid, Meyers, Neligh, and Richards, 1949), and it has been suggested that it may be present even lower in the intestine. This raises the question whether gastric atrophy is the primary lesion in Addisonian pernicious anaemia or only part of a widespread tissue defect. The whole problem of the metabolism of vitamin B_{12}, including its interaction with intrinsic factor and its relationship to the bacterial flora of the bowel, is receiving much attention at present (Dyke, Hind, Riding, and Shaw, 1950 ; Hall, 1950).

In all cases in which macrocytic anaemia occurs some years after extensive gastric resections there exists the possibility of coincidence. This requires serious consideration after partial gastrectomy, for of all the many patients who have been submitted to the operation relatively few have been reported to develop macrocytic anaemia, and coincidence probably cannot be absolutely ruled out in any single case. Statistical probability, however, makes coexistence very unlikely (Bloomfield and Polland, 1935). The incidence of macrocytic anaemia in patients who have survived three or more years after total gastrectomy is so great as to exclude all possibility of coincidence.

The present case has several interesting features. No previous record has been found of macrocytic anaemia following gastrectomy performed for the effects of corrosive poisoning, but Alsted (1937) reported a case in which "pernicious anaemia" developed seven years after destruction of the gastric mucosa by nitric acid.

Two years after operation, and in the absence of symptoms, the red blood cell count was 3.51 millions per c.mm. ; the anaemia was normochromic and macrocytic. Although erythropoiesis was normoblastic, many of the normoblasts were prematurely haemoglobinized. These changes were thought to represent an early stage of a "liver-factor" deficiency anaemia. It is rare for a patient with Addisonian pernicious anaemia to seek advice before the red blood cell count is considerably lower than 3.5 millions per c.mm., and information on the earliest marrow changes is scanty. Penati and Saita (1938) stated that megaloblasts first appear when the number of erythrocytes has fallen to 3.5 millions per c.mm. The findings in our case support the contention that macrocytosis is the earliest haematological abnormality in pernicious anaemia and is present before the onset of symptoms. The megaloblastic anaemia, diagnosed approximately three years after cessation of prophylactic liver therapy, appeared identical to Addisonian pernicious anaemia except for the absence of bilirubinaemia.

Treatment with vitamin B_{12} produced striking clinical improvement, but the haematological response, though good, was less than expected. The peak of the reticulocyte rise (28%) was only 69% of that expected in Addisonian pernicious anaemia of the same severity from potent liver extract given intramuscularly (Isaacs and Friedman, 1938). It has been shown, however, that the reticulocyte response is not always a good measure of activity (Murphy, 1933 ; Fullerton, 1945) ; a better yardstick is the rate of increase of the red blood cells. The rise of the red blood cells in the first 15 days compared unfavourably with that expected in Addisonian pernicious anaemia, whether judged by the formula of Della Vida and Dyke (1942) for parenteral liver extract, or by that of Ungley (1949) for pure crystalline vitamin B_{12} obtained from liver.

According to Ungley (1949) a single injection of 40 μg. of crystalline vitamin B_{12}, in a patient with Addisonian pernicious anaemia and initial red blood cell count of 0.95 million per c.mm., is expected to raise the count to 2.73 millions in 15 days. This compares with a figure of only 1.7 millions per c.mm. in our case. The biggest discrepancy, noted by Ungley (1949) in 63 cases, between the estimated and observed increase was 0.79 million per c.mm. Even if allowance has to be made for a slight difference in the therapeutic effect of the preparations used by Ungley and ourselves the evidence suggests that the megaloblastic anaemia which followed gastrectomy in this case was not identical with Addisonian pernicious anaemia.

Further support for this hypothesis is provided by the poor final effect of vitamin B_{12} therapy. Ungley (1949) found, in 32 cases of Addisonian pernicious anaemia, that the maximum amount of vitamin B_{12} required to raise the red cell count above 4.5 millions per c.mm. was 140 μg. In the present case a total of 320 μg., in divided dosage at weekly intervals, failed to increase the count above 3.8 millions per c.mm. After remaining around this level for six weeks a sharp rise followed the addition of folic acid. The inability of vitamin B_{12} to bring about complete remission after its very beneficial initial effect was unexpected. Larger doses might have proved more successful.

The relationship between vitamin B_{12} and folic acid is a much vexed question and has recently been reviewed by Girdwood (1950). One striking fact is that no satisfactory human case of megaloblastic anaemia has yet

been described which responded haemopoietically to vitamin B_{12} after failing to respond to folic acid. The experimental work of Heinle, Welch, and Pritchard (1948) is of considerable interest. They produced megaloblastic anaemia in pigs by feeding a highly purified diet free of extrinsic factor and containing succinylsulphathiazole and a crude folic acid antagonist. This diet was calculated to produce a deficiency both of vitamin B_{12} and of pteroylglutamic acid. A pig rendered anaemic by this method first responded incompletely to liver extract containing no folic acid, but two months later failed to respond to daily injections of liver extract; folic acid then produced an excellent effect. This is a sequence of events somewhat similar to that obtained in our patient. Those authors concluded, from this and other experiments, that in these experimental conditions neither the anti-pernicious-anaemia factor (regarded as identical with or similar to vitamin B_{12}) nor folic acid can function haemopoietically in the absence of the other, and that both substances are essential for the maturation of erythrocytes.

Israëls and Sharp (1950) suggested that the megaloblastic anaemias can be divided into two groups, depending on the effect of treatment. The first is typified by Addisonian pernicious anaemia, which responds well to parenteral or oral liver preparations, vitamin B_{12}, and folic acid. The second group includes "pernicious anaemia" of pregnancy, the megaloblastic anaemia of non-tropical sprue, and probably tropical sprue as well: these conditions react satisfactorily to folic acid but not to parenteral liver extracts or vitamin B_{12}, at least in doses suitable for the first group. The present case appears to fall between these two groups, for, although by no means refractory to vitamin B_{12}, the response was suboptimal compared with that expected in Addisonian pernicious anaemia. Folic acid is unnecessary at any stage in Addisonian pernicious anaemia treated with vitamin B_{12} and usually essential from the outset in non-tropical sprue. In our case it was required only for "topping up" after vitamin B_{12}.

Final evaluation of the respective functions of folic acid and vitamin B_{12} must await further work. Evidence collected from various clinical experiences, such as that described in this paper, may eventually help to solve the problem.

Summary

A case of megaloblastic anaemia following total gastrectomy performed for the effects of corrosive poisoning is described.

The pathogenesis of the anaemia is discussed in the light of the classical theory of erythropoiesis.

Striking clinical improvement followed vitamin B_{12} therapy, but the haematological response was suboptimal compared with that expected in Addisonian pernicious anaemia. The addition of folic acid brought about complete haematological remission.

The effect of treatment suggested that this type of megaloblastic anaemia and Addisonian pernicious anaemia are not identical, although morphologically similar.

The relationship of the anaemia to other megaloblastic anaemias, as regards treatment with vitamin B_{12} and folic acid, is discussed.

We wish to thank Professor C. F. W. Illingworth for permission to publish this case and Professor J. W. McNee for advice. The blood investigations in 1944 and 1946 were performed by Dr. Peter McKenzie, and we are indebted to him for permission to quote his results.

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HAEMOPOIETIC ACTIVITY OF VITAMINS $B_{12}c$ AND $B_{12}d$ IN PERNICIOUS ANAEMIA

BY

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After the isolation of vitamin B_{12} from liver (Lester Smith and Parker, 1948; Rickes *et al.*, 1948a), and the subsequent discovery that the vitamin could be obtained from botanical sources (Rickes *et al.*, 1948b), physicochemical studies showed that there are other members of the vitamin B_{12} group of factors. Vitamin $B_{12}a$, the reduction product of vitamin B_{12} (Kaczka, Wolf, and Folkers, 1949), has been shown probably to be identical with vitamin $B_{12}b$ (Brockman *et al.*, 1950; Anslow *et al.*, 1950), and crystalline vitamins $B_{12}c$ and $B_{12}d$, derived from *Streptomyces griseus*, have been described (Lester Smith, 1950, 1951; Anslow *et al.*, 1950; Buchanan *et al.*, 1950). These factors appear to be chromatographically distinct from one another; in addition they have different properties in the microbiological assay (Lester Smith, 1951).

This paper records the primary haematological responses in pernicious anaemia to vitamin $B_{12}c$ (nine cases) and vitamin $B_{12}d$ (five cases).

Material and Methods

The patients, in varying stages of relapse, had clinical signs and symptoms consistent with a diagnosis of pernicious anaemia. Laboratory investigations showed macrocytic anaemia associated with a megaloblastic marrow and histamine-alcohol-fast achlorhydria. Nine patients were females and five males, their ages ranging from 34 to 78 years. Five of them had received previous liver therapy with good results, but had relapsed on discontinuation of injections. No case in this series showed objective evidence of severe neurological involvement, but several of them had some degree of sensory disturbance. No recent therapy had been given before admission to hospital, and they all took "mixed British diets." When in hospital they were on "ordinary" ward diet, and were given no other therapy. Two cases had to be tested as out-patients; other variables were so introduced, but no additional haematinic was known to be taken.

When the red cell count showed a continued fall with no increase in reticulocytes over 2%—this period varying according to the severity of the case—a single dose of 20 μg. of test material was injected intramuscularly. Regular haematological examinations were made during the 14 days after the injection. The gain in the red cell count in 15 days was taken as the measure of haematological improvement (Della Vida and Dyke, 1942).

The average weekly gain in red cells observed was compared with the so-called "average satisfactory" or "expected" figure obtained from Della Vida and Dyke's formula:

$$I = 0.93 - 0.214\ Eo$$

where I = millions average weekly gain in R.B.C. per c.mm. during the first two weeks of therapy, and
Eo = initial number of R.B.C. in millions per c.mm.

No elaborate statistical analysis is worth while for so small a series of cases (cf. Ungley, 1949): the simple recording of observed results in relation to the standard 20-μg. intramuscular dose of the two new vitamin B_{12} factors is the object of this report.

On "day 0" and "day 15" venous blood was collected in Wintrobe's oxalate. Haemoglobin estimations were made either with a grey wedge photometer (King *et al.*, 1948), which was N.P.L. tested, or by Haldane's method. Both instruments were calibrated so that 100%

TABLE I.—*Haematological Responses in 9 Cases of Pernicious Anaemia Given a Single Dose of 20 μg. Vitamin $B_{12}c$ Intramuscularly*

Case No.	Age and Sex	Day of Treatment	Hb g. per 100 ml.	R.B.C. (mill. per c.mm.)	Maximal Reticulocyte Response	P.C.V. (%)	M.C.V. (μ^3)	M.C.H.C. (%)	Bilirubin mg. per 100 ml.	Average Weekly Gain in R.B.C. (mill. per c.mm.) Compared with Della Vida and Dyke's Formula		Remarks
										"Expected"	"Observed"	
1	48 M	0 15	8·7 12·0	2·30 2·93	12% (6th day)	27·5 37·0	120 123	32 32	0·9 <0·5	0·44	0·31	
2	58 F	0 15	7·6 10·2	1·90 2·71	16·5% (4th day)	23·0 33·0	121 122	33 31	1·1 <0·5	0·52	0·41	
3	68 F	0 18	8·3 11·1	2·37 3·52	—	26·5 —	122 —	31 —	1·2 —	—	—	Treated as out-patient
4	34 M	0 15	7·8 10·8	1·86 3·05	25% (7th day)	25·0 35·0	134 115	31 31	1·3 —	0·54	0·60	
5	49 M	0 15	14·1 15·1	3·37 3·85	7% (4th day)	42·0 43·0	128 112	34 35	<0·5 —	0·21	0·24	
6	65 M	0 15	5·8 9·6	1·30 2·22	30·5% (5th day)	16·5 28·0	126 126	35 34	1·1 0·6	0·65	0·46	
7	43 M	0 15	11·5 13·0	2·81 3·49	—	34·5 38·0	123 108	33 34	1·0 <0·5	0·34	0·34	Treated as out-patient
8	64 F	0 15	5·3 8·6	1·2 2·3	26·5% (5th day)	16·5 29·0	138 126	32 30	1·8 <0·5	0·67	0·56	Developed iron deficiency
9	37 F	0 15	8·4 9·5	2·2 2·8	16·5% (5th day)	28·0 31·5	128 112	30 30	0·7 <0·5	0·46	0·30	Associated iron deficiency (see text)

TABLE II.—*Haematological Responses in 5 Cases of Pernicious Anaemia Given a Single Dose of 20 μg. Vitamin $B_{12}d$ Intramuscularly*

Case No.	Age and Sex	Day of Treatment	Hb g. per 100 ml.	R.B.C. (mill. per c.mm.)	Maximal Reticulocyte Response	P.C.V. (%)	M.C.V. (μ^3)	M.C.H.C. (%)	Bilirubin mg. per 100 ml.	Average Weekly Gain in R.B.C. (mill. per c.mm.) Compared with Della Vida and Dyke's Formula		Remarks
										"Expected"	"Observed"	
10	78 F	0 9 15	5·8 6·7 8·4	1·46 1·86 2·45	19·5% (7th day)	19·5 — 30·0	133 — 122	30 — 28	1·0 <0·5	— —	— —	Intercurrent pulmonary collapse. Second injection given 9th day (see text)
11	76 F	0 15	6·5 10·3	1·47 3·0	28·5% (7th day)	19·0 33·5	129 112	34 31	1·3 0·9	0·615	0·765	Marrow normoblastic 48 hours after injection
12	63 F	0 15	7·6 11·8	1·65 2·93	16·0% (6th day)	23·5 37·0	142 126	32 32	1·1 <0·5	0·567	0·640	Marrow normoblastic 48 hours after injection
13	69 F	0 15	5·0* 9·0	1·03 2·75	21·5% (6th day)	13·0 30·0	126 109	38* 30	1·7 <0·5	0·710	0·860	Marrow normoblastic 48 hours after injection
14	69 F	0 15	7·0 10·2	1·70 3·20	26·5% (5th day)	20·0 33·0	118 103	35 31	1·8 1·2	0·566	0·750	Marrow normoblastic 72 hours after injection

* Probably too high readings due to bilirubinaemia.

Hb was equivalent to 14.8 g. Hb per 100 ml. The same instrument was used for all determinations on any one case. When performing red cell counts in an improved Neubauer chamber at least 500 cells were counted. Packed cell volumes were calculated by Wintrobe's method and reticulocytes of capillary blood were estimated by a "dry" cresyl-blue method—counterstaining with Leishman's stain.

Results.—The haematological responses over a 15-day period to a single dose of 20 μg. of material are recorded in Tables I and II. The response in Case 11, treated with vitamin $B_{12}d$, is shown in the Chart.

Discussion

The recorded results must be considered in the light of the known errors associated with haematological methods (Biggs and Macmillan, 1948 ; Dacie, 1950). In the present series of cases no attempt at statistical analysis is deemed permissible, but further cases will be studied and those of the present group available for follow-up will be observed over a further period of time.

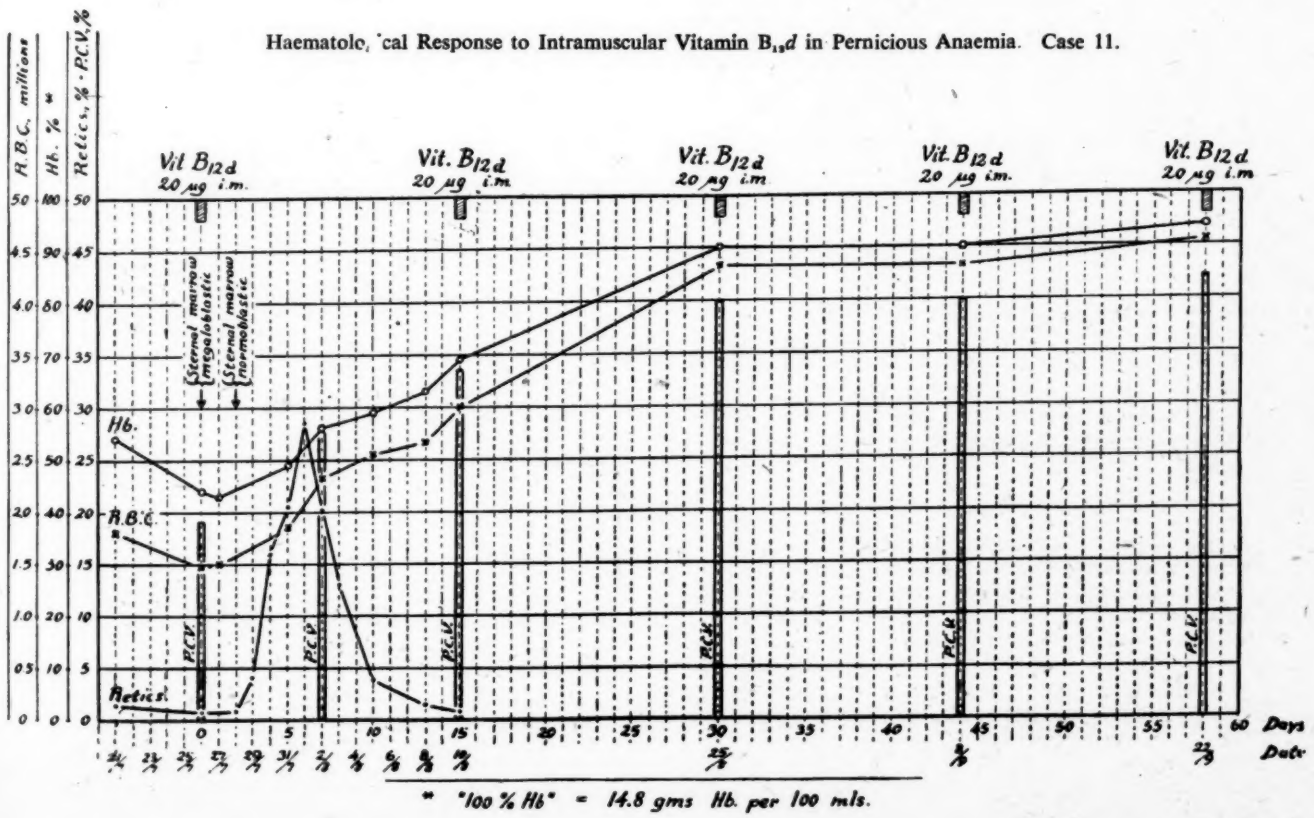
Vitamin $B_{12}c$ given in a single dose of 20 μg. caused a haematological response in the nine cases studied—reticulocytes reaching a peak on the fourth to the seventh day and the formula of Della Vida and Dyke for the 15-day increase being satisfied in three of those eight cases to which it was applicable. In Case 3 the criterion was satisfied on the 18th day ; as the patient could not come into hospital she was tested as an out-patient. Case 9, that of a married woman aged 37, had a severe menstrual period during the time of test and showed signs of an associated iron deficiency. After the 15-day test, fortnightly injections of 40 μg. of vitamin $B_{12}c$ together with a course of oral ferrous sulphate caused rapid and progressive clinical improvement with lessening of neurological symptoms and glossitis. The blood values were within a so-called "normal range" in two months. Normal range is notoriously difficult to define (see Dacie, 1950), but is here taken as being at least 13.8 g. of Hb per 100 ml., over 4.5 million R.B.C. per c.mm., and a P.C.V. of over 40%. Other cases reached so-called "normal range" within six to ten weeks with a dose of 20 to 40 μg. of vitamin $B_{12}c$ intramuscularly every fortnight after the test period. All showed a striking improvement, with gain in strength, appetite, and weight.

Of the five patients treated with vitamin $B_{12}d$, four have fully satisfied the criteria of Della Vida and Dyke for the 15-day period, reticulocyte peaks occurring on the fifth to the seventh day. The remaining patient (Case 10) also had a good response, but she was a frail old lady with intercurrent pulmonary collapse. A second injection of 20 μg. was given on the ninth day and the formula was not applicable. She was one of the first cases to be treated with this factor, and only two doses of it were at that time available for test. Subsequently there was further recovery on another vitamin B_{12} preparation. Vitamin $B_{12}d$ on primary clinical trial seems very active. It is too early for conclusions to be drawn from a follow-up, but those cases being investigated show progressive clinical and haematological improvement at the time of writing on doses of 20 μg. of vitamin $B_{12}d$ at fortnightly intervals.

Summary

Nine cases of pernicious anaemia in relapse have been treated with crystalline vitamin $B_{12}c$ and five cases with crystalline vitamin $B_{12}d$. Both of these factors are clinically active. Marked clinical improvement, with considerable relief of glossitis and lessening or disappearance of subjective nervous symptoms, occurred. It is too soon to

Haematolc, 'cal Response to Intramuscular Vitamin $B_{12}d$ in Pernicious Anaemia. Case 11.



draw further conclusions, but a more detailed report on the value of these and other fractions and concentrates of the vitamin B_{12} group will be published in due course.

My thanks are due to Dr. E. Lester Smith and his associates, of Glaxo Laboratories Ltd., Greenford, for supplies of differentiated members of the vitamin B_{12} group: to those physicians, pathologists, and general practitioners who referred relapsed cases of pernicious anaemia for investigation; and to my technical staff, particularly Mr. S. E. Louland, for their assistance.

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TWO CASES OF PERNICIOUS ANAEMIA TREATED WITH VITAMIN $B_{12}d$

BY

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As described by Lester Smith on page 151, vitamin B_{12} concentrates produced during the fermentation of *Streptomyces griseus* contain a number of factors having biological properties like those of vitamin B_{12}. It is clearly of importance to know whether a concentrate standardized microbiologically against pure vitamin B_{12} is of the same therapeutic activity as if it consisted entirely of that substance. To establish this it is necessary to compare all the individual factors with vitamin B_{12} and to discover whether or not their ratios of human to bacteriological activity are constant.

To further this object two cases of pernicious anaemia were treated with crystalline vitamin $B_{12}d$ at the Walsall General Hospital. One of these (Case 1) also afforded an opportunity of comparing the potency of this substance with that of a liver extract that had been used on the same patient during a previous admission to hospital.

Case 1

A woman aged 67 was admitted to hospital on October 30, 1948, with the symptoms and physical signs of pernicious anaemia. Laboratory findings were: Hb, 56%; R.B.C., 2,240,000 per c.mm.; C.I., 1.25; M.D.R.C., 8.4 μ (approx.); C.V., 35%; M.C.V., 156 μ^3; reticulocytes, 0.8%; W.B.C., 4,800 per c.mm. The blood film showed marked anisocytosis and poikilocytosis. The van den Bergh test gave a positive indirect reaction of 10 mg. per litre. A test meal revealed that no free HCl was present.

On November 3, 1 ml. of "examen" B260A was given intramuscularly: the response obtained completely fulfilled Della Vida's criterion for satisfactory treatment.

The patient made an excellent recovery, and on return home attended the out-patient department regularly until April 7, 1949, when she elected to receive further treatment from her own doctor. However, she did not see him until the middle of July, 1950, when he was called in for the first time and found her extremely ill, being very pale, dyspnoeic, and oedematous. Only then was it discovered that she had had no anti-anaemic treatment for roughly 14 months.

On her readmission to hospital on July 20 she was in a very much worse condition than before, her blood picture being: Hb, 40%; R.B.C., 1,600,000 per c.mm.; C.I., 1.25; reticulocytes 1%. She said that she felt better than she had done a few days previously, and her own doctor, who saw her on the day of admission, confirmed this. With the 1% reticulocyte count and these observations by the patient and her doctor, it was thought that she was in mild remission.

On July 22, 1 ml. (10 μg.) of vitamin $B_{12}d$ was given intramuscularly, and she again showed an excellent response to the treatment, although the reticulocytes did not quite reach the expected 20%. This was thought to be due to the fact that she was in remission when the treatment was begun. The increase in red cells slightly exceeded the expected response according to Della Vida's formula (Fig. 1). She recovered well and was discharged from hospital on August 12.

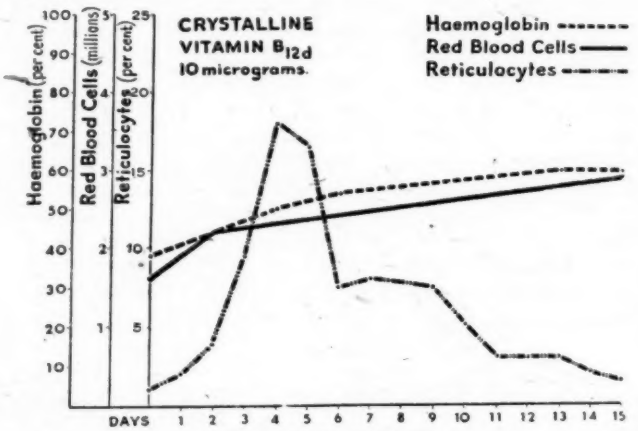

FIG. 1.—Chart of Case 1.

Case 2

A man aged 60 was seen at the out-patient department on June 20, 1950, in an obviously very anaemic condition and with early signs of subacute combined degeneration. The laboratory findings were: Hb, 33%; R.B.C., 1,300,000 per c.mm.; C.I., 1.27; M.D.R.C., 7.8 μ (approx.); C.V., 14%; M.C.V., 108 μ^3; W.B.C., 3,800 per c.mm. The van den Bergh test showed a faint positive indirect reaction of 8 mg. per litre. The test meal revealed no free HCl.

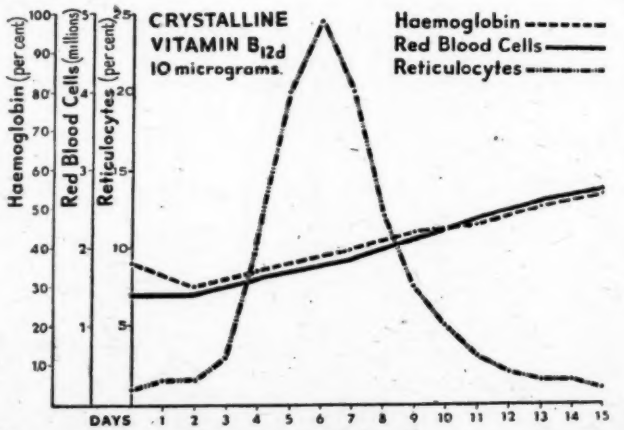

FIG. 2.—Chart of Case 2.

On July 31, 1 ml. (10 μg.) of vitamin $B_{12}d$ was given intramuscularly and an excellent response was obtained, the expected reticulocyte count and the expected red cell total both being reached (Fig. 2). This result again showed that 10 μg. of vitamin $B_{12}d$ had maximum anti-anaemic-factor activity.

Summary

Two cases of pernicious anaemia have been successfully treated with vitamin $B_{12}d$ in the very small dosage of 10 μg. Both showed the anti-anaemic activity to be of the same order as that of crystalline vitamin B_{12}.

In one case 10 μg. of vitamin $B_{12}d$ gave the same response as 1 ml. of examen, having full anti-anaemic activity at that dose level.

The crystalline vitamin $B_{12}d$ used in the treatment of the two cases described above was supplied by Glaxo Laboratories Ltd., to whom I wish to express my thanks.

MUCUS CATHETERS*

BY

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The removal of mucus from the respiratory passages is a basic step in treating asphyxia of the newborn. Without a clear airway no success can be expected from other methods of resuscitation. Relatively little attention is often paid, however, to the means by which the air-passages are to be cleared. Unsatisfactory instruments are widely used. A review of current methods, especially with reference to the risk of infecting the child, therefore seems overdue.

Historical Notes

Special tubes have long been used for blowing into babies' throats. An early example was Pugh's (1754) air pipe, "made of a small common Wire, turned very close (In the Manner Wire-Springs are made) and covered with thin soft Leather." Chaussier (1785) designed a metal tube for passage into the trachea. Quills and the stems of churchwarden pipes served the same purpose.

During the nineteenth century simple tubes of metal or rubber came into use for preliminary suction also. The chief patterns were the "tracheal pipes" of Blundell (1834) and Chaussier. The unpleasantness of sucking mucus into the mouth was soon recognized but long tolerated. Traps were indeed foreshadowed by Dewees (1825), who wrote, "Might not a properly constructed syringe be highly useful in removing the obstructing mucus?", but no such instrument appeared until 1877. Tarnier then adopted the insufflator, operated by rubber bulb, which bears the name of Ribemont-Dessaignes (1900).

Champneys (1886, 1911) advised that the air-passages be cleared without suction, by tilting the child's head back and blowing into the mouth. The mucus, having gravitated towards the posterior nares, was thus expelled through the nose. "In rare cases," he added, "it may be necessary to pass a catheter into the trachea. If passed 3½ in. (9 cm.) from the lips, it will be below the glottis and above the bifurcation of the bronchi. The chest should be compressed with one hand and the operator should blow down the catheter, which will cause an up-draught in the trachea and empty it of mucus."

A trap was added to the old tracheal pipe about 1898, when Carton, of Dublin, invented his mucus catheter (FitzGibbon, 1923; no original description traced) with closed end and lateral apertures. Cowell's (1912) design was similar but had a terminal opening. These metal types, with the glass-bulbed patterns which appeared after 1920, remain in common use in Britain. In the United States, De Lee's glass mucus trap has been used for about 50 years.

Methods of Removing Mucus

Drainage by gravity, holding the baby up by the feet, is now considered unwise in cases of severe asphyxia, when intracranial haemorrhage may be present. The blowing method is likely to infect the child. Champneys (1886) himself quoted Reich's account of an outbreak of tuberculous meningitis due to mouth-to-mouth insufflation by a phthisical midwife, and non-tuberculous infection is also important. Suction may be applied by mouth, by rubber bulb, or by a Venturi tube operated by water, by a cylinder of compressed gas (Saher and Salt, 1943), or by electric motor (Roberts, 1949).

The electric and gas-cylinder devices are said to be effective, but are costly and not available in the home. The water suction pump is also confined to institutions and is inconvenient, involving long tubing and usually an assistant to stand by the tap. Excessive negative pressures, which may damage the child, must be guarded against with these instruments. The recoil of a strong rubber bulb produces adequate negative pressure, but the tube must be removed from the throat, probably several times, to renew the vacuum. It is less convenient than mouth-suction.

Of all methods, for convenience, simplicity, and accurate control, mouth-operated mucus catheters are still usually preferred. Their continued use, however, can be recommended only if they are of effective design and properly used.

Essential Features

It is suggested that a mucus catheter must fulfil three conditions.

1. *It Must Have an Efficient Trap.*—Many catheters are not fully protective. Some are too small. In others the inlet is at the bottom of the trap; then, when thin fluid partly fills the space, air is drawn through it and froth is sucked up. One common pattern has no trap but consists of two rubber tubes with a glass connexion of equal diameter. Through this device mucus and meconium often reach the operator's mouth, and it is remarkable that so many doctors and nurses tolerate it. Mucus, as well as being unpleasant, may infect the attendant.

2. *The Tip Must be Soft and Flexible.*—The infant's mucous membrane is easily damaged, and the asphyxiated baby, if livid and hypertonic, or flaccid and lying head downwards on a slope, may lurch suddenly. Rubber tubes should therefore replace those of metal or glass

3. *It Must Not Infect the Child.*—A mucus catheter which becomes blocked is commonly cleared by blowing

*Based on a paper read before the Scottish Paediatric Society on June 16, 1950.

and then used again : a dangerous practice, for the tube has become contaminated by organisms from the attendant's throat. This risk of carrying infection to the child has only recently been emphasized (Munro Kerr and Chassar Moir, 1949 ; Ellis, 1950).

How can the danger be eliminated ? A plug of cotton-wool in the mucus trap is unsatisfactory, as it is easily clogged. Deflection of the air-stream by tubes within the trap is only a partial safeguard. Clearly, whenever the instrument becomes choked it should be laid aside and a fresh sterile one taken. At least three, therefore, should be boiled and placed ready at every confinement. "The practice of blowing through a blocked mucus extractor is inexcusable" (Ellis, 1950).

A further precaution is to use the mucus catheter with discretion It tends to be employed at every birth, without good reason and with needless repetition. Many babies, after all, need no help in clearing their airways. Premature and feeble infants, so prone to infection, call for particular care.

A mucus catheter should also be simple, easily cleaned, and cheap but not unduly fragile, and the trap should be transparent.

Bacteriological Tests

The object of the tests was to assess the danger of infecting the child and the protection afforded by different patterns of mucus trap.

1. An operator with a healthy throat was selected. Five different types of mucus catheter and six samples of 1 ml. of broth were sterilized. A was the mucus catheter with no trap ; B had a simple trap which did not deflect the air-stream ; the traps of C, D, and E thoroughly deflected the air-stream through them. With each catheter, 1 ml. of broth was sucked up and blown out three times, then incubated for 36 hours in a poured blood–agar plate. A control sample of broth was exposed to the air and similarly incubated. This series of tests was carried out on three separate days, and the following number of colonies of organisms grown is the average of the three occasions.

Pattern	Average No. of Colonies
A. No trap	Uncountable
B. Simple trap	8
C. Experimental	5
D. Aberdeen	3·5
E. Middlesex Hospital (large trap)	11
F. Control	4

In cultures A to E the organisms were mainly *N. catarrhalis, Str. viridans,* and *Staph. albus,* with some haemolytic streptococci, *Staph. aureus,* and diphtheroids. In the control cultures they were *Staph. albus* and diphtheroids.

2. With an operator recovering from a heavy cold, similar tests were made. (A throat swab produced on culture a profuse mixed growth of *Str. haemolyticus* and *Str. viridans.*) First, one short breath was blown through each mucus catheter on to a blood–agar plate.

Pattern	No. of Colonies After 24 Hours
No trap	6 *Str. viridans*; 2 contaminants
Middlesex Hospital	1 *Str. viridans*; 2 contaminants
Control plate	2 of contaminants

1-ml. samples of broth were then sucked up and blown out twice with each instrument and incubated in poured blood–agar plates.

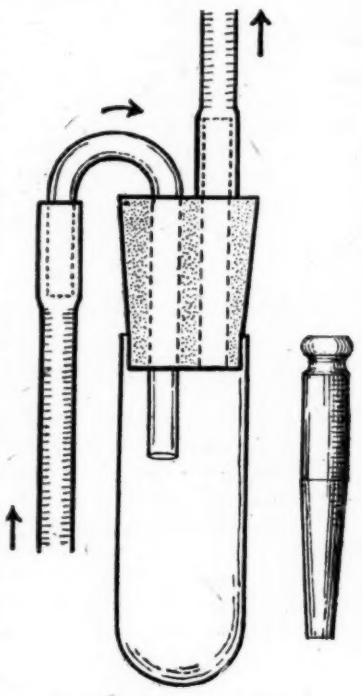
Pattern	No. of Colonies After 24 Hours
No trap	9 haemolytic streptococci; 75 *Str. viridans*
Middlesex Hospital	1 *Str. viridans*
Aberdeen	1 *Str. viridans*
Control	1 contaminant

3. Similar results were obtained in the labour ward. Mucus was repeatedly sucked from an infant's throat with the same mucus catheter and each sample cultured separately. The serial cultures showed that with repeated aspiration and blowing the contamination rapidly became heavy. Twelve babies were thus observed.

Our conclusions are that the mucus catheter which has no trap is dangerous, that any trap reduces contamination from the attendant's throat, and that no pattern of trap prevents it.

A New Design

If the above criteria are accepted, many current types of mucus catheter must be regarded as obsolete. To satisfy these criteria, the pattern illustrated has been developed at Aberdeen Maternity Hospital.



The trap is of hardened glass. The rubber bung carries two glass tubes, one bent upon itself. The inlet tube projects ½ in. (1.25 cm.) into the trap, the outlet being flush with the bung. On each end is a length of rubber tubing, the upper tube being firm enough to make a mouthpiece unnecessary. The lower tube is smaller and softer, but not so thin-walled as to collapse readily. For ordinary use plain tubing is preferred to a narrow catheter with a lateral aperture. Its cut end has not been found harmful, but the rounded tip of a rectal tube can be substituted if desired. Occasionally, when tracheal suction is needed, a thin tube can be attached by a tapered connexion of metal (as illustrated) or glass. A Magill's silk-web endotracheal tube, No. 4, or a rubber catheter may be used, according to the method of intubation. The combination may be employed for De Lee's method of resuscitation, by intratracheal insufflation with the attendant's breath (De Lee and Greenhill, 1947). The force required is well stated in a detailed account by Mathieu and Holman (1929). It should, "with the lips pursed to whistle, be felt on the wet finger about 3½ to 4 in. (9 to 10 cm.) from the mouth," and the operator should puff about forty times a minute. This can be commended as an emergency measure only, to treat extreme asphyxia in domiciliary practice when the risk of infection must be subordinated to that of immediate death. In hospital practice, mechanical insufflation with known pressure is preferred.

The Aberdeen mucus catheter is supplied by Archibald Young and Son, Ltd., 57–61, Forrest Road, Edinburgh, with the choice of a plain or rounded tip.

The term "catheter" can be correctly used in this connexion, and is preferable to the less pleasing "extractor," "evacuator," or "aspirator."

Summary

A mucus catheter operated by mouth-suction is the most convenient means of clearing the throat of the newborn baby, but an efficient mucus trap must protect the user.

The danger of carrying infection to the child is demonstrated. After a mucus catheter has been blown through it should never be replaced in the baby's throat.

Mucus catheters of effective design can be cheaply made of glass and rubber, and several should be provided at every delivery.

I wish to thank Professor John Craig and Professor Dugald Baird for advice and criticism; Dr. Leslie W. Fraser, lecturer in bacteriology, University of Aberdeen; and Mr. William Cowie, technician, University of Aberdeen, who designed the mucus trap which was finally adopted.

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CHRONIC RENAL DISEASE WITH SECONDARY HYPERPARATHYROIDISM

BY

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It is now well established that a close relationship exists between renal disease and parathyroid hyperfunction. Thus many cases of primary hyperparathyroidism show evidence of disturbed renal function, and, pathologically, calcium deposits in the kidneys are a feature. These may be intratubular, peritubular, or interstitial, and be accompanied by cellular infiltration and fibrosis. The usual result is interference with tubular function, leading to urine of constant low specific gravity, polydipsia, and polyuria. The large amount of calcium excreted in the urine in this condition often results in renal calculus formation, and this may lead to obstruction or infection.

However, the functional relationship between the kidneys and the parathyroid glands is a reciprocal one. The subject is reviewed by Anderson (1939). Bergstrand (1921) noted the frequency with which parathyroid enlargement acompanied renal damage, and Gilmour and Martin (1937), in an extensive statistical study, found the parathyroid glands to be of a higher mean weight in renal disease than in other disease groups. They also noted that the glands had a higher percentage of parenchyma per unit of weight in renal disease than occurs normally. In rare instances of chronic renal disease this hyperplasia may be sufficiently well marked to give rise to clinical manifestations of hyperthyroidism. In still fewer instances bone lesions similar in every respect to the osteitis fibrosa of primary hyperparathyroidism have been present. Such cases have been reported by Hubbard and Wentworth (1920–1), Albright *et al.* (1937), and Herbert *et al.* (1941). The renal lesion has varied from case to case. Chronic nephritis, chronic pyelonephritis, and polycystic disease have been described, but in all cases the renal insufficiency has been long-standing and severe.

In children, as in adults, long-standing renal insufficiency may lead to parathyroid hyperplasia and hyperfunction. Langmead and Orr (1933) reported a case of renal rickets in which all four parathyroid glands were grossly enlarged and the histological changes in the bones presented a composite picture of classical osteitis fibrosa and of true rickets. Gilmour (1947) found similar histological changes in the bones of seven out of eight subjects aged 3 to 17 years with chronic renal disease. In five of these the parathyroid glands were definitely hypertrophied.

Metastatic calcification is an interesting phenomenon which has an undoubted association with both renal disease and hyperparathyroidism. In this condition calcium salts are deposited in previously normal tissues. In addition to the kidneys, the common sites of calcium deposition are the arterial walls, the heart, the mucous membrane of the stomach, and the skin and subcutaneous tissues (calcinosis). The condition may be produced experimentally in animals by overdosage with parathyroid extract or with vitamin D. In both instances deposition of calcium salts in the kidneys may lead to severe renal impairment. Essentially the same pathological picture has been produced in man by excessive administration of vitamin D. The association of metastatic calcification with renal disease has excited much interest since the original description of the condition by Virchow (1855). He observed five cases, in all of which there was more or less severe nephritis. Four of these were accompanied by destructive bone disease, but in one there were no demonstrable skeletal changes.

Barr (1932) stated that it was difficult to find cases of metastatic calcification in which a renal element could be excluded. Herbert *et al.* (1941) collected 19 cases of metastatic calcification from the literature, and 16 of these were associated with gross renal disease. In 11 of these 16 there was evidence of parathyroid hyperplasia, and in only one case was parathyroid hyperplasia definitely excluded. In three cases unassociated with gross renal disease the parathyroid glands were normal. Gilmour (1947) described three well-marked cases of metastatic calcification occurring in chronic renal disease. In each of these there was marked parathyroid hyperplasia and the bone changes of osteitis fibrosa.

In the case of chronic nephritis reported below, gross enlargement of the parathyroid glands was found in association with metastatic calcification and bone changes of osteitis fibrosa.

Case Report

The patient, a married woman aged 44, gave a history of scarlet fever in childhood. In 1927, at the age of 22, she developed swelling of the face and legs, and was treated in hospital for three months as a case of nephritis. She then remained well, and married in 1931. One year later a pregnancy was terminated because of persistent vomiting, and sterilization was performed by ligation and division of both Fallopian tubes.

She was first admitted to the Queen Elizabeth Hospital on January 23, 1949, for dental treatment. She had complained of lack of energy and poor appetite for the previous few months, and on admission presented a picture typical of advanced renal insufficiency.

Examination revealed a thin woman with a pale puffy face. Hypertension (blood pressure 200/110) and cardiac enlargement were present. A rough systolic murmur was heard all over the praecordium, with maximal intensity at the apex. The urine was of constant low specific gravity and contained albumin and granular casts.

The patient was discharged on February 15, only to be readmitted on September 16. She then complained of very severe pain in the toes of the right foot of three weeks' duration. Her general condition had deteriorated markedly in the seven months since her previous admission, and there was now persistent vomiting and low urinary output. All five toes of the right foot were cold, blue, and insensitive—the seat of a dry gangrene. Pulsations were absent from the popliteal, posterior tibial, and dorsalis pedis arteries of the right leg. The patient gave a history of intermittent claudication affecting both legs and growing steadily worse over the previous year. More recently similar pain produced by exertion—for example, by combing the hair—and relieved by rest had occurred in the forearms.

Gallop rhythm was audible over the praecordium, and the apical systolic murmur, heard first in January, 1949, was much rougher and was accompanied by a coarse thrill.

A few days after admission the patient lapsed into coma and, with increasing nitrogen retention, died on September 25.

Laboratory Data.—A blood count on January 26 showed: red cells, 3,180,000 per c.mm.; haemoglobin, 58% (Haldane); colour index, 0.93; and on September 16: red cells, 2,230,000 per c.mm.; haemoglobin, 42% (Haldane); colour index 0.94. The blood urea was 158 mg. per 100 ml. on January 28, 195 mg. on February 19, and 365 mg. on September 23. The blood proteins on September 19 were albumin 4 g.%, globulin 1.4 g.%. The serum calcium was 10.9 mg. per 100 ml. on September 20 and 13.3 mg. on September 23. The serum phosphorus (as inorganic phosphate) was 8.7 mg. per 100 ml. on September 20 and 11.9 mg. on September 23. On September 20 the plasma carbon-dioxide combining power was 30 volumes % and the plasma *p*H 7.36.

Radiological Investigations.—A radiograph of the chest in January, 1949, showed cardiac enlargement and marked calcification in the aortic arch. In September, in addition to these findings, a radiograph of the chest showed marked calcification in the arteries of the thyroid axes and of the arteries in the lateral chest wall. There were also heavy calcium deposits in both lung fields, spreading out from the hila. A radiograph of the limbs on September 17 showed heavy calcification of the arterial tree, involving not only the main vessels but also the finer muscular branches. The branches of the common iliac arteries were similarly involved. A radiograph of the head showed calcification in the walls of the ophthalmic and meningeal arteries. There was diffuse mottling of the skull, giving an even "ground-glass" appearance characteristic of osteitis fibrosa. The skeleton elsewhere was radiographically normal.

Post-mortem Examination

This was carried out on September 26. The body was that of a middle-aged woman; weight 49.1 kg.

Heart.—This was moderately enlarged owing to left ventricular hypertrophy (weight 385 g.). The aortic valve showed slight calcification, which appeared to have originated in the sinuses of Valsalva. The pulmonary and tricuspid valves were normal. The mitral valve was heavily calcified and there was an irregular mass of calcified material 1.5 cm. in diameter at the junction of the cusps. The coronary vessels showed a fine nodular calcification.

Aorta.—Advanced atheroma with large calcified plaques was found immediately above the commissure and in the region of the great vessels. Atheroma was less marked in the descending thoracic portion, but in the terminal abdominal aorta calcification was very marked. The lumen was slightly reduced and the wall almost devoid of elasticity. Histologically advanced medial and intimal degeneration with heavy calcification was present.

Arteries.—There was moderate calcification of the proximal portion of the common iliacs. The external iliacs and proximal femorals were almost devoid of calcification. The subclavian arteries were calcified. Both popliteals were severely calcified. The right radial artery showed much calcification and recent thrombosis. Portions of the right femoral, left profunda femoris, left popliteal, digital, and basilar arteries were examined histologically. All showed advanced medial degeneration and fibrosis, and in many places degeneration of the intima also, with fibroblastic proliferation and atheromatous changes. In some of the arteries—for example, the radial—there was almost complete replacement of the vessel wall by calcified material. In general, the calcification seemed to follow degenerative changes in the arteries; and, broadly, was most intense where degeneration was most advanced.

Lungs.—There was partial collapse of the bases of lobular distribution. Mucous bronchiolitis was present, but no consolidation. The walls of the bronchi near the hilum were calcified. Histologically there was massive calcification of the bronchial cartilage, especially in the larger branches, but no vascular calcification. A few patches of calcareous material were found in the alveoli.

Kidneys.—Both were extremely small (total weight 125 g.). The subcapsular surfaces were finely granular. The cortex was reduced in width but the vessels were not unduly prominent. Histologically, the appearance conformed with "nephritis repens" type 2 (Russell, 1929). In the main the calcium deposits were limited to the vessel walls, though there were occasional deposits in the fibrinoid glomerular tufts and in the interstitium.

Parathyroids.—Four large glands were found. Three were embedded in the substance of the thyroid gland and measured 10 by 8 mm.; 8.5 by 6 mm., and 9 by 6 mm. (estimated weight 382 mg., 195 mg., and 221 mg. respectively). The superior left parathyroid was found in its normal position and weighed 419 mg. The histology corresponded with Gilmour's type 4. The structure was compact and lobular, water clear, and transitional cells predominated over dark principal cells. There were numerous foci of oxyphil cells and many areas of columnar-celled alveolar structure. Arterioles in the vicinity showed calcification.

Skeleton.—The skull, shaft of femur, sternum, and a portion of rib were examined. To the naked eye only the skull was abnormal. It was definitely thickened, and softer and easier to cut than normal. Microscopically all the bones showed lacunar resorption by osteoclasts, with fibrosis around the affected area—a picture typical of osteitis fibrosa. In many places the process could be clearly shown to have started in the Haversian canals, with progressive enlargement of these as the bone was eroded. Except in the skull, in which haemopoietic and adipose marrow was absent, the marrow proper was but little affected. There was only slight evidence of osteoplastic reaction, and the condition was evidently one of considerable activity and short duration. There was no evidence of rachitic changes.

Discussion

The essential features of this case of chronic nephritis were the gross enlargement of the parathyroid glands, the bone changes of osteitis fibrosa, and the extensive and widespread degeneration and calcification of the arterial tree. This latter feature resulted in diminished

blood supply and ischaemic muscle pain in all four limbs for many months before death. Finally, arterial narrowing led to vascular occlusion in the right leg, and this led to gangrene of the toes of the right foot. Heavy deposits of calcium in the mitral valve brought about stiffening of the cusps, and was presumably the cause of a very rough systolic murmur and thrill.

In this patient, as in other patients with renal hyperparathyroidism, there were marked phosphorus retention and low plasma carbon dioxide combining power. The serum calcium was normal (10.9 mg. per 100 ml.) until two days before death, when it rose to 13.3 mg. According to Albright and Reifenstein (1948) a tendency to low serum calcium occurs as an adjustment to phosphorus retention. Parathyroid hyperplasia takes place in response to the stimulus of this low calcium level. The increased production of parathyroid hormone leads to the mobilization of calcium from the bones and then the serum calcium is raised to normal or higher from the earlier low level. The serum phosphorus, however, remains high, as the usual action of parathyroid hormone in producing a phosphorus diuresis cannot occur because of the renal disease. The blood and tissues now become over-saturated with calcium phosphate, and this may lead to the precipitation of calcium salts in the tissues of the body.

Finally, it is interesting to note that in this case three out of the four enlarged parathyroid glands were found embedded in the thyroid gland. This raises the possibility of difficulty in the surgical treatment of primary hyperparathyroidism in which an adenoma or one or more hyperplastic glands may be hidden in the substance of the thyroid gland. However, this is not a common occurrence, and Norris (1947) records that out of 281 cases in which parathyroid adenomata were removed in the treatment of hyperparathyroidism the tumour was found within the thyroid gland in only nine instances.

Summary

The relationship between chronic renal disease and parathyroid hyperfunction is discussed and the literature is reviewed, with special reference to the occurrence of metastatic calcification and osteitis fibrosa.

A case is reported of chronic nephritis with parathyroid hyperplasia, showing widespread arterial calcification and the bone changes of osteitis fibrosa.

I wish to thank Professor W. Melville Arnott for permission to publish this case, Professor J. W. Orr for the pathological report, and both for their criticism and help.

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CRYOGLOBULINAEMIA IN MULTIPLE MYELOMATOSIS

BY

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This article describes an unsuspected case of multiple myelomatosis in which the diagnosis was first suggested by the accidental finding of cryoglobulinaemia. This term, proposed by Lerner and Watson (1947), means literally "cold globulin in the blood," and implies the presence in the plasma of a globulin which precipitates or solidifies on cooling. In the recorded cases this usually took place at about 30° C., and it may produce partial or complete solidification of the blood. The phenomenon is reversible on warming to 37° C., and the changes may be repeated indefinitely, although they occur slowly.

I have been able to trace about a dozen cases in the literature. Rörvik (1950) gives a review of nine of these, with a tenth case report; Shapiro, Ross, and Moore (1943) reported a case which showed the essential features, although they did not use this name; and Hill, Dunlop, and Mulligan (1949) described a case. In most cases the primary disease is multiple myelomatosis, but there is evidence to show that such globulins are also found in endocarditis lenta (Lerner and Watson, 1947), in humans and dogs with kala-azar, in nephrosis (Wertheimer and Stein, 1944), and in infective arthritis (Rörvik, 1950).

Case Report

A retired gardener aged 64 was admitted to hospital on January 4, 1950, for a skin condition—phrynoderma—which subsequently proved to be due to vitamin-A deficiency. He had had this complaint a year previously, and had been cured by the administration of vitamins; he admitted that he had had a very deficient diet, and his plasma showed a deficiency of vitamin A. At the time of admission, however, he felt well except for this complaint.

On January 12 blood was taken into a Wintrobe oxalate bottle for a blood count. This showed an anaemia (60%), with a normal colour index, a normal white cell count and distribution, and a corrected sedimentation rate of 22 mm./hour (haematocrit 28%). The haematologist stated: "The red cells show a marked tendency to auto-agglutination, with a very rapid sedimentation rate. There is also an unusual phenomenon, spontaneous clotting in an oxalate bottle after one to two hours on the bench." The protein constitution of the blood was queried on this account. On the following day I went to the ward to obtain venous blood to investigate the plasma proteins, using a syringe sterilized in the laboratory, and therefore cold. The veins were prominent, but only a few drops of blood were obtained before the flow ceased. A large needle boiled up in the ward was substituted and 30 ml. of blood was readily obtained. The significance of the temperature difference between the two needles was not appreciated at the time. The blood was placed in the incubator (37° C.), and the serum separated off in the usual way. By Harrison's (1949) method, using 27.79% ammonium sulphate for the precipitation of globulin, and biuret estimation, the serum proteins were: albumin, 3.8 g.%; globulin, 8.2 g.%; total, 12 g.%.

It was then observed that the serum had solidified on the bench. This suggested that the clotting referred to by the haematologist and the blocking of the first needle were in fact processes of solidification due to cooling. Investigation showed that the serum set slowly into a soft solid white opaque mass at 22° C., and melted into a normal clear

pale-yellow serum at 30° C. This change could be repeated indefinitely. When a drop was allowed to cool on a slide a mass of small burr-like crystalline deposits separated, the individual mass being composed of fine needle-like crystals arranged radially. These disappeared again on warming.

Since such high globulin figures are found in only a few conditions—commonly sarcoidosis, kala-azar, and myeloma—and there was nothing to indicate the first two, investigations were put in hand to confirm the third. Radiographs of the skeleton showed a generalized osteoporosis without any localized defects. Bence-Jones protein was not found in the urine at this or any other time, though a slight albuminuria was constant. The serum calcium was 11.2 mg. and the uric acid 2.9 mg. per 100 ml. It is of interest to note that the thymol turbidity test of Maclagan (1947) gave a result of 1 unit, since the gamma globulin was afterwards shown to be high. Sternal puncture was next performed; this decided the diagnosis, showing a great preponderance of plasma-type myeloma cells. The patient died on February 28.

Necropsy.—The bones showed the expected changes; the clots in the vessels were particularly opaque and tenacious, a feature on which von Bonsdorff *et al.* (1938) remark. Sections of the bone marrow showed the most extensive deposits of plasmocytoma, and sections of blood clot the same crystalline masses as those referred to above. Death was due to bronchopneumonia.

The original serum was now further investigated. Because of the white colour of the solid serum, the total ether-extractable matter was estimated. It proved to be 1.1 g.% against 1.5 g.% in pooled normal serum, suggesting that there was no excess of fat. Next the proteins were fractionated (see Table), using the method of Kibrick and Blonstein

	Patient's Serum (g.%)	Average of 6 Normal Persons (g.%)
Total protein	12·0	7·2
Albumin	1·9	4·3
Globulin	10·1	2·9
Alpha	1·9	1·0
Beta	1·2	0·9
Gamma	7·0	1·0

(1948), which gives results close to those obtained by electrophoresis. The estimation was completed by the method of Gornall, Bardawill, and David (1949). The normal figures were obtained from six normal people, and showed close agreement among themselves.

Discussion

The case described did not present any of the clinical features that have been directly attributed to cryoglobulinaemia. The case of Rörvik (1950) showed bleeding and ulceration of the ears and limbs, particularly following exposure to cold; that of Hanson and Faber (1947) had Raynaud's syndrome; that of Wintrobe and Buell (1933) had retinal thrombosis and Raynaud's syndrome; one of Lerner and Watson's cases (1947) had purpura; and in this connexion it is interesting to note that Waldenström (1944) collected seven cases of "purpura hyperglobulinemica," two of which, while they did not have cold precipitable globulins, had uveoparotitis, a feature of sarcoidosis.

Von Bonsdorff *et al.* (1938), who described one of the earliest cases of cryoglobulinaemia, made the following observations on the serum in their case: (1) clumps formed spontaneously in Hayem's solution; (2) the serum agglutinated both its own and other red cells: (3) clot retraction was incomplete and slow; (4) the serum separated into two layers, the lower third being turbid and containing needle-like crystals; (5) the total protein was 9–10 g., with a raised globulin; (6) the molecular weight of the crystalline protein was about 200,000; and (7) the Takata–Ara and formol-gel tests were positive. In my case very rapid sedimentation with clumping of the red blood cells took place. Clot retraction was poor on the bench, but normal in the 37° C. incubator, a feature which Rörvik also noticed.

Separation into layers is a point which several authors have remarked upon. It varies in degree, sometimes the whole volume becoming solid and depositing crystals, as in my case and in Rörvik's, and sometimes only a layer being deposited, as in the cases of Wintrobe and Buell, von Bonsdorff *et al.*, and Hill *et al.* The small quantities of cryoglobulin to be expected in the infectious diseases may be discovered only after prolonged observation in the icebox.

Nature of the Abnormal Protein

The method of choice in separating and classifying proteins at present is electrophoresis. By this method Adams *et al.* (1949) have examined the sera of 41 cases of myelomatosis; they found sometimes an excess of gamma globulin, sometimes of beta globulin, sometimes of an intermediate fraction, and sometimes no abnormality. Kekwick (1940), in five cases, found three with an excess of gamma globulin and one with excess of beta globulin. Lüdin (1947) reports two cases with a rise in the alpha fraction. Gutman *et al.* (1941), using Howe's method, found all combinations of level of euglobulin and the pseudoglobulins in myelomatosis, but assert that in all the other diseases in which hyperglobulinaemia occurs the excess protein is solely euglobulin. In my case, by the method of Kibrick and Blonstein (1948), the excess protein fell in the gamma fraction, and in four cases of cryoglobulinaemia which have been examined by electrophoresis (Rörvik) the protein was in each instance a euglobulin falling into the gamma fraction.

The crystals in the present case were needle-shaped, as in all the other recorded instances except that of von Bonsdorff, in which some were boat-shaped. Needle-like crystals have been found in the plasma cells in a case of myeloma (Steinmann, 1949) and also flat plates (Neumann, 1949). Sikl (1949) found flat plates in the kidneys. None of these was observed in the present case.

Summary

A case of multiple myelomatosis is reported in which the diagnosis was suggested by the finding of cryoglobulinaemia. The nature of the abnormal protein in this condition is discussed.

My thanks are due to Dr. E. Colin Jones for permission to report this case and to Dr. L. R. Janes for laboratory facilities.

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Medical Memoranda

Faecal Fistula and Bilateral Strangulated Hernia in an Infant

Strangulated inguinal hernia in an infant does not occur very often. The following case report presents unusual features and is worthy of record.

CASE REPORT

A Portuguese male child, aged 7 weeks and weighing 6 lb. (2.7 kg.), was brought to hospital with the following history. He was born prematurely after seven months' gestation, weighing 3½ lb. (1.6 kg.). Shortly after birth an umbilical hernia and an absent testis on the left side were noticed. Ten days before admission to hospital a tender red swelling, which was considered to be cellulitis of unknown origin, developed in the left groin. It was treated with systemic penicillin and hot compresses and appeared to settle down, but after a week it became more obvious. The day before admission a small white bleb appeared on the scrotum. This burst and discharged faeces but no pus. Throughout these 10 days the child had been reasonably well, with no vomiting, and the bowels had opened regularly.

On examination the patient was fairly well and had no evidence of dehydration. A large red swelling was present in the left groin extending down into the left scrotum. At the lowest point in the scrotum a small opening discharged yellow semi-solid faeces. The abdomen was not distended. There was an umbilical hernia about 1½ in. (3.8 cm.) in diameter. A diagnosis was made of a strangulated hernia of the Littré or Richter type.

Operation.—Under ethyl chloride and open ether anaesthesia, an incision was made over the upper part of the swelling. All tissues were very oedematous and the layers could not be defined. The hernial sac was identified and opened. An attempt was made to withdraw the contents from the sac. These were found to consist of caecum and the appendix. The distal end of the caecum was adherent and part of the wall had sloughed. The appendix was not strangulated. The contents were separated from the sac, the caecal wall was repaired in two layers, the hernial sac closed, the abdominal wall repaired with nylon mattress sutures, and the scrotum drained. The child stood the operation well.

Feeding was resumed as soon as possible, 1 oz. (28 ml.) of half-strength milk being given every two hours, alternating with glucose water two-hourly. "Aureomycin," 125 mg., was given four-hourly in a teaspoonful of condensed milk. The child made an uninterrupted recovery. The stitches were removed on the tenth day, by which time the scrotal wound was healed, and he was discharged from hospital 14 days after admission. Three weeks later the patient was readmitted with a strangulated right inguinal hernia, which was successfully treated immediately. The umbilical hernia was repaired at the same time to prevent a third crisis.

This case is of interest, for it presents an example of intestinal malrotation, with the caecum and appendix appearing in a left-sided hernial sac. It is also of interest because the child remained so well during his 10-day illness despite the fact that part of the intestine had become strangulated and had actually sloughed, producing a faecal fistula.

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Unusually High Blood Sugar in a Boy

Noteworthy features in the following case were an unusually high blood glucose concentration, eventual stabilization on 5 units of insulin daily, and maintenance of good progress for more than three years.

CASE REPORT

The patient, a boy aged 8, an only child whose birth was normal of normal parents, was underdeveloped, weighing only 36 lb. (16.3 kg.). He had seemed tired and listless for two or three months, and recently frequency of micturition and some thirst but no polyuria had occurred. There had been no apparent loss of weight, and the chief trouble had been "colds" and septic teeth, for which sulphathiazole (4 g.) had been given on the day before admission.

He was admitted to hospital on January 15, 1947, in profound diabetic coma of 42 hours' duration. Dehydration was pronounced, acetone was detectable in the breath, his blood pressure (by palpation) was extremely low, temperature 94° F. (34.4° C.), respirations 28, and pulse 132. Urine, by catheter, gave strongly positive reactions for glucose and acetone. The blood glucose concentration was 1,076 mg. per 100 ml. by Folin–Wu micro-technique using unlaked blood—Herbert and Bourne's method (Harrison, 1937a); carbon-dioxide-combining power was 10 ml. of CO_2 per 100 ml. plasma by Van Slyke's volumetric technique (Harrison, 1937b).

Treatment was begun with 20 units of soluble insulin half-hourly, continuous intravenous 5% glucose in saline, and 10 g. glucose, with 5 g. sodium bicarbonate given hourly by stomach tube. In the first 20 hours the patient received 820 units insulin, 380 g. glucose, 100 g. sodium bicarbonate, and 3,600 ml. intravenous saline, but the blood glucose concentration persisted at a level well over 1,200 mg. per 100 ml. and reached the value of 2,100 mg. per 100 ml. at the 16th hour.

Despite persistence of gross hyperglycaemia, similar treatment was continued to the 23rd hour, when it was changed to 20 units insulin three-hourly; later it was varied to 10 units two-hourly. Glucose, 10 g., was continued hourly by mouth, and intravenous glucose in saline was continued up to the 30th hour, when the child regained consciousness at a blood glucose concentration of 226 mg. per 100 ml. and carbon-dioxide-combining power of 100 ml. CO_2 per 100 ml. plasma. In all, from the 20th to the 44th hour, he received 240 units insulin and 340 g. glucose; during that period the blood glucose concentration diminished rapidly, reaching 70 mg. per 100 ml. at the 36th hour.

In the next six days, while 20 units insulin twice daily was continued and glucose feeding was gradually replaced by a 1,200-calorie diet, blood glucose concentrations varied between 91 and 188 mg. per 100 ml. A sudden rise of blood glucose to 500 mg. per 100 ml. was met by increasing the insulin to 26 units twice daily. Contrary to expectations at this time, the patient showed marked sensitivity to insulin, and two days later developed hypoglycaemic coma, with blood glucose 31 mg. per 100 ml. The dose of insulin was promptly reduced to 15 units, then to 5 units twice daily, and this last dosage was maintained for 25 days while the diet was built up to 2,000 calories. The patient then appeared to be well stabilized and a glucose tolerance test (25 g. oral) showed: fasting, 138 mg. per 100 ml. blood

(glycosuria 1%); ½ hour, 157 mg. (1%); 1½ hours, 273 mg. (2%); 2½ hours, 220 mg. (5%). Insulin was then reduced to 5 units once daily, and the patient was discharged 44 days after admission.

Since then, good progress has been maintained and he has been supervised for more than three years. Soluble insulin therapy was changed to globin insulin (8 units once daily), with appropriate diet for a child aged 11 years, height 48 in. (122 cm.), and weight 56 lb. (25.4 kg.). There have been no relapses.

COMMENT

Joslin *et al.* (1946) reported a blood glucose concentration of 1,680 mg. per 100 ml. in a patient who recovered. The maximum recorded value in a patient who recovered appears to be 1,850 mg. per 100 ml. (Dillon and Dyer, 1935). A value of 2,060 mg. per 100 ml. was found by Lawrence (1934) in a patient two hours after 40 units of insulin had been given; this patient died.

Our patient, after receiving 660 units insulin and 320 g. glucose in 16 hours, attained a blood glucose concentration of 2,100 mg. per 100 ml.; this was at 2 a.m. Assuming that the "active volume of tissue fluid" was initially 0.5 that of the body weight, and allowing for the administration of nearly 3 litres of intravenous saline, calculations show that more than half the glucose administered had already been disposed of up to this time. In the next few hours, continued treatment rapidly restored the blood (and tissue fluid) glucose concentration to normal.

We wish to thank Miss E. Radovitch, formerly house-physician, for her co-operation, and Dr. H. L. Milles, under whose care the patient was admitted, for his help and encouragement in preparing this memorandum.

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Unusually High Blood Sugar in an Adult

The following case illustrates well that ketosis is the real enemy in diabetic coma, and that frequent blood-sugar estimations are essential.

CASE REPORT

A woman aged 67 was admitted to hospital unconscious on December 16, 1949, soon after midday. She was well known in the local diabetic clinic, being usually well stabilized. When seen in June, 1949, she was on a diet containing 150 g. of carbohydrate and having 26 units of soluble insulin, plus 8 units of protamine-zinc insulin each morning. She had failed to keep subsequent appointments, but her urine record up to December 14 showed mainly green tests. Her history included a perirenal abscess opened three years previously, and occasional attacks of urinary infection.

The patient had spent the previous day in Worthing, and had developed extreme frequency of micturition there. She came back that night, and knew no more until she woke up in hospital. She had almost certainly had no insulin on the 16th.

At 1.30 p.m. blood was taken, a fast-running normal saline intravenous drip was set up, and 50 units of soluble insulin were given intramuscularly. When I first saw her, at 1.45 p.m., she was deeply stuporous, but could appreciate stimuli. Her temperature was 97° F. (36.1° C.), pulse 80, and respirations 22. There was not a strong smell of acetone and the respiratory movements were not deep and mechanical. She was not flushed, but the eyeball tension was lowered.

At 4 p.m. it was reported that the blood sugar had been 2.000 mg. per 100 ml. at 1.30 p.m., so 100 more units of soluble insulin were given intramuscularly and 20 units intravenously. The pathologist, Dr. J. McMurray, checked this amazing figure on the same specimen of blood and made it 1,980 mg. At 6 p.m. the blood sugar was 1,020 mg. per 100 ml.

About 7 p.m. the intravenous drip stopped after she had had 1,500 ml. and had taken 16 oz. (454 ml.) by mouth. Owing to other emergencies, and the very difficult state of her veins, it was not started again until about 9.30 p.m. By this time she was conscious but still restless. On this occasion 4.3% glucose in N/5 saline was used. At 9.30 p.m. the blood sugar was 50 mg. per 100 ml.; this was reported by 10 p.m., and 4 ml. of 25% glucose solution was given into another vein (with great difficulty) and 30 g. of glucose by mouth. A further 30 g. of glucose was given at 11 p.m. by mouth.

From then on the patient made steady progress. A radiograph of her chest was normal, but a catheter specimen of urine grew a heavy growth of *Bact. coli*. It was rendered sterile after a course of "sulphatriad." She was discharged on January 10, 1950, on her usual 150-g. carbohydrate diet and insulin, 34 units soluble, plus 16 units P.-Z.

The recorded urine tests (catheter) during the critical period were as follows.

Urine Tests During Critical Period

Time	Benedict	Rothera	Gerhardt
16/12.49:			
12.30 p.m. ..	Red	+++	++
4 „ ..	„	+++	++
7 „ ..	Orange	+++	+
9 „ ..	Khaki	++	Nil
12 midnight ..	Dark green	++	„
1 a.m.	Green	+	„
3 „	Orange	Trace	„
5 „	„	Slight trace	„

COMMENT

This patient's good fortune lay in the comparatively slight degree of ketosis, which was apparent at once in her condition, and was borne out by the rapid disappearance of ketone bodies from the urine. This occurred in spite of the break in giving intravenous fluids. She responded very rapidly to insulin despite the very high blood sugar. This figure cannot be in doubt, as it was checked, and the 4-p.m. specimen was also high although she was responding excellently to treatment. One wonders if the unusual sensitivity to insulin at such a high blood sugar and the failure to attain the expected degree of ketosis were related.

I am indebted to Dr. E. J. Glynn for permission to describe this case, which he asked me to see, and to Dr. J. McMurray for the blood-sugar estimations.

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Reviews

ORTHOPAEDIC SURGERY

Modern Trends in Orthopaedics. Edited by Sir Harry Platt, M.D., M.S., F.R.C.S. (Pp. 497; 222 figures. £2 5s., postage 1s. 6d.) London: Butterworth and Co. 1950.

This book is an important edition to the literature of orthopaedic surgery in this country. The editor's contribution—a short chapter on the evolution and scope of modern orthopaedics—reflects his wide knowledge of teaching and training both at home and abroad. The next 13 chapters are a series of essays by authoritative contributors on problems in which advances are occurring or have been recently consolidated, and they make fascinating reading. Though each author has treated his subject in his own characteristic way, the essays fall broadly into two classes—creeds and reviews. The best example of a statement of personal belief comes in the second chapter from John Charnley's vigorous writing on fracture treatment, with the emphasis on mechanical principles and the biology of callus. Entirely different in approach is the review of the bone dystrophies by H. Jackson Burrows in the last and longest chapter of 70-odd pages, and it is masterly.

The intermediate text varies considerably in style, but there is hardly a dull page. How refreshing it is, for instance, to read the blunt opinions of D. Ll. Griffiths on certain vascular lesions: "The best advice in such circumstances is still the old one, that the 6-hour tourniquet should be amputated off"; or again: "The facile diagnosis of costoclavicular compression is nevertheless being made far too often, and upon two diagnostic features which are both certainly fallacious." G. R. Girdlestone's experience of tuberculosis of bone and joint, Ronald Furlong's vignettes of tendon injuries, and H. Osmond-Clarke's bird's-eye view of the scoliosis problem make other chapters full of general interest.

So much for the text, but what of the illustrations? Truly the salt of this book hath lost his savour, for hardly any of the radiographs retain their original detail. This may not matter so much in the chapter on scoliosis, but, when it comes to tumours of bone, injuries of the spine, and the vagaries of callus formation, the deficiencies of the blocks are only too apparent. Until this technical fault is corrected—a matter surely of no difficulty in a country which has good reason to be proud of its medical illustration—this work will not win its full credit. Nevertheless, no orthopaedic surgeon should miss reading it, and the postgraduate student will be grateful for many of the chapters.

K. I NISSEN.

HASTENING EVOLUTION

The Art of Scientific Investigation. By Professor W. I. B. Beveridge. (Pp. 171. 10s. 6d.) London: William Heinemann. 1950.

This book, which is written by an active research worker, is one of the most fascinating I have read for a long time, for the author discusses not only research but mental processes in general. C. S. Lewis once said to me, referring to a world-famous scientist, "I can't understand how X came to be so famous, he always seems to me so stupid." C. S. Lewis is the author of the *Screwtape Letters* and similar books, in which reason and logic are used with great ingenuity, but the plain fact is that this is not the way by which scientific knowledge advances. The virtue of Beveridge's book is that it explodes the myth of the austere scientist working by the cold light of reason and shows that successful research is largely a matter of chance and empiricism. Reason has a vital part to play in checking ideas and results, but very little in their production. Research, in fact, is one of the creative arts, and one is almost tempted to call it the acceleration of evolution.

After discussing training and preparation for scientific work and the experimental method, Beveridge underlines the part played by chance and misconception in successful discovery and the role of the imagination and intuition. This is followed by chapters on the strategy of research and observation. Beveridge suggests that the discovery of a new technique is at least as meritorious as the discovery of a new fact or a new generalization. In these days, when the training of the young worker is long and the middle-aged are soon overtaken by routine duties and administration, it is well to be shown once again that one of the most important conditions for creative work is freedom from other problems or interests competing for attention. Indeed, time is essential in research, as W. B. Cannon pointed out.

> "The investigator may be made to dwell in a garret, he may be forced to live on crusts and wear dilapidated clothes, he may be deprived of social recognition, but if he has time, he can steadfastly devote himself to research. Take away his free time and he is utterly destroyed as a contributor to knowledge."

As a matter of history, Pierpont Morgan said that he could do a year's work in nine months, but not in a year, a long time before the similar remark attributed here to Simon Flexner, and Pierpont Morgan did a lot of important work in his time.

L. J. WITTS.

CONGENITAL HEART DISEASE

Congenital Heart Disease. By James W. Brown, M.D. (Lond.), F.R.C.P. Second edition. (Pp. 344; 128 figures. £1 10s.) London: Staples Press. 1950.

The first edition of this book (1939) was very well received both in this country and abroad, and until Taussig's volume was published in 1947 it had no competitor. Dr. Brown now gives us a second edition, much extended and revised. This too will be welcomed, and it deserves even higher praise than the first. Erudition and simplicity are harmoniously wedded, and more than 700 references are incorporated in the text without detracting from its fluency. The development of the heart and great vessels, always a difficult subject, has been particularly well handled, and embryological errors resulting in the common anomalies are clearly described. There is also a good discussion on the various factors that may be responsible for such errors.

The author's practical experience of congenital heart disease both at the bedside and in the post-mortem room is probably unique in this country, and it forms the basis of his book. Few will criticize him for standing firmly on his own ground. It is indeed remarkable that a work on this subject can command such respect without paying homage to modern techniques: thus, there is not a single angiocardiogram among the illustrations; there is very little information about physiological data obtained by means of cardiac catheterization; and electrocardiograms show only the

three conventional leads. But what may be lost by these omissions is made up by a wealth of other material; and it is just these riches, which Dr. Brown has so ably presented for us, and which might so easily have been lost, that make the book so valuable.

Students of congenital heart disease may take issue with him over a number of clinical and physiological details, but this is inevitable in any rapidly advancing subject. What is more certain is that any such student will have to buy the book, for he will need to refer to it often.

PAUL WOOD.

SEX ANATOMY

Human Sex Anatomy. By Robert Latou Dickinson, M.D., F.A.C.S. A Topographical Hand Atlas. Second edition. Medical Aspects of Human Fertility Series issued by the National Committee on Maternal Health, Inc. (Pp. 145 text, 175 plates; illustrated. £3 16s. 6d.) London: Baillière, Tindall and Cox. 1949.

The first edition of this book, which appeared in 1933, has been widely quoted. More data and illustrations are now added. The text comprises only 130 pages and, even if not everywhere up to date, includes some interesting information not easily obtained elsewhere. There is also a useful bibliography.

The greater space (175 pages) is devoted to detailed illustrations of the male and female genitalia under different physiological circumstances, and variations in their anatomy according to sexual practices. Some of the plates are exceptionally good, and it would be difficult to find their equals. They are clearly based on close observations and careful records of large numbers of men and women. In places, however, it is difficult not to question whether the work does not represent misplaced energy and enthusiasm. None will gainsay the author's contention that knowledge of the sex act is important to marital harmony, but do the exact dimensions of the phallus, or its angle of erection, merit such careful study and delineation? Does it serve any useful purpose to devote several pages to illustrations of the detailed relations of the male and female genitalia under the conditions of coitus in different postures? The place for this book is the reference library rather than the dining-room shelf.

T. N. A. JEFFCOATE.

ROCHESTER MEDICAL CENTRE

The Quarter Century. A review of the first 25 years, 1925–50. School of Medicine and Dentistry, Strong Memorial Hospital, Rochester Municipal Hospital. (Pp. 144; illustrated. Price not stated.) Rochester, New York: University of Rochester. 1950.

The Rochester medical centre was founded in 1920 on the initiative of the General Education Board of the Rockefeller Foundation. Inquiries had convinced the board that another first-class medical school was needed in the western part of New York State, and Rochester was chosen as its seat because it already possessed a university of high standing founded in 1850. The medical school was built and endowed mainly through the generosity of Mr. George Eastman and the General Education Board. The associated teaching hospital was provided by the two daughters of Mr. and Mrs. H. A. Strong, and the city of Rochester later built its municipal hospital on university land. The school was opened to medical students in 1925; in dentistry only postgraduates are accepted.

The organization of the centre was entrusted to a pathologist, Dr. G. H. Whipple, who still retains his original appointments as dean of the school and professor of pathology. A pupil of Welch and Osler at the Johns Hopkins, he soon gathered round him an able group of professors, largely Hopkins men. From the start it was decided to aim at the closest possible co-operation between clinical and non-clinical departments in both teaching and research; for this reason the medical school, teaching hospital, and municipal hospital were housed in a single large building with centralized services.

This book, edited by a committee under the chairmanship of Professor W. O. Fenn, is described as a "family document," and appropriately contains many portraits and other photographs. The history of the centre is described by the dean, and the teaching hospital by its director. The growth and work of the departments, including one of atomic energy, are outlined by the various professors. These essays are of much more than "family" interest; they give a fascinating account of medical progress during the past twenty-five years and together constitute a valuable and stimulating contribution to medical education. All concerned had to enter on their work with nothing but a vision of what a modern medical school should be; if there was any failure, there were no predecessors to blame. This book shows that there has been no need of scapegoats: fidelity to the concept of medicine as a single science has been extraordinarily fruitful in both teaching and research. The school is producing good doctors; this is not surprising, for the teachers are investigators who have already made it one of the leading medical research institutions of the world.

RAYMOND WHITEHEAD.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Fifty Years of Medicine. A Symposium from the *British Medical Journal*. (Pp. 330. 15s.) London: British Medical Association. 1950

Advances in Internal Medicine. Edited by W. Dock, M.D., and I. Snapper, M.D. Vol. 4. (Pp. 549. $10.) Chicago: Year Book Publishers. 1950.

Diagnostic Procedures and Reagents. Edited by R. S. Muckenfuss, M.D. 3rd ed. (Pp. 589. $6.) New York: American Public Health Association. 1950.

Methods in Medical Research. Edited by R. W. Gerard, M.D., Ph.D. Vol. 3. (Pp. 312. $7.) Chicago: Year Book Publishers. 1950.

Die Praxis der Modernen Narkose. By Dr. H. Moser. (Pp. 195. $5.70.) Vienna: Wilhelm Maudrich. 1951.

Sesiones Dermatologicas en Homenaje al Professor Luis E. Pierini. (Pp. 521. No price.) Buenos Aires: Año del Libertador General san Martin. 1950.

The second edition of Professor John Caffey's *Pediatric X-ray Diagnosis* (Chicago: Year Book Publishers, Inc. London: H. K. Lewis and Co. $22.50 or £8 9s.) has been extensively revised and expanded. An increase of nearly 400 new figures brings the total to over 1,000—often with more than one *x*-ray photograph in each illustration. The result is a valuable atlas in which the normal is discussed before pathological variations are set out. The text contains useful and critical comments, and the bibliographies at the end of the sections are an important part of the book. It is beautifully printed, and obviously must have been expensive to produce. Even so, the price seems high—and higher still for British purchasers.

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THE OLD MINISTER AND THE NEW

Mr. Aneurin Bevan did his best to make himself disliked by the medical profession, and, by and large, he succeeded. From the point of view of the Government he had the requisite measure of political adroitness to put on the Statute Book Acts which revolutionized the practice of medicine. In this, of course, he was assisted by the fact that some such reform was approved by all political parties and by the fact that the B.M.A. had supported the idea of a comprehensive medical service for 100% of the population. Mr. Bevan, unfortunately, never rose above being a clever politician, and at critical moments failed to become the statesman who should reconcile conflicting interests and try to understand the other man's point of view. He was too much the prima donna who wanted to astound the political theatre with his rhetorical brilliance. The medical profession will not easily forget his vicious attack on it in the House of Commons in the early part of 1948, nor his attempts to sow discord between general practitioners and consultants, nor his rudeness in negotiation. More especially has the medical profession resented his delaying tactics in avoiding giving general practitioners a fair deal under the terms of the Spens recommendations. His continued evasion of this problem has brought things to such a pitch that general practitioners are now seriously making plans for withdrawal from service if their proper claims are not realistically investigated and met. Apart from all this, the National Health Service has as yet failed in its main object—to bring the full resources of medicine within immediate reach of the whole population. It is true that certain obstacles have been in the way, such as the shortage of nurses and beds, shortage of materials and labour for the reconstruction of hospitals, confusion over the part to be played by health centres even if they could be built. But the economics of the Service have got completely out of control, and the administrative machine is creaking loudly. As a consequence there is widespread dissatisfaction in the medical profession and among the general public. No wonder Mr. Bevan was anxious to be transferred to another ministerial post.

Mr. H. Marquand, his successor, has an unenviable task. It is at all events satisfactory that he is a Minister of Health and not a Minister of Housing as well, although the transfer to the Minister of Town and Country Planning of housing and of responsibilities in relation to local government will during the transition period dislocate the work of the Health Ministry. Mr. Marquand has a distinguished academic record as a historian and as an economist, and comes into his new office from the Ministry of Pensions, having previously been Secretary for Overseas Trade and Paymaster-General. The first thing we may hope for is an improved relationship between the new Minister and the medical profession. Doctors will be the first to recognize that Mr. Marquand has come into a doubtful inheritance, but will, we believe, be prepared to work with him in an attempt to solve the enormous problems ahead so long as he deals with the profession as a body of responsible persons anxious to do efficiently the work for which they have been trained. The establishment by the B.M.A. of a General-Practice Review Committee underlines what is the crucial issue in medicine to-day. Another sign of this is the appointment by the Central Health Services Council of a committee to study general practice under the N.H.S. The general practitioner is tired of being called the backbone of the profession and treated as the tail-piece. Whatever may be the internal difficulties of the Ministry of Health as a result of the reorganization of its work, and though the new Minister must have time to learn his new job, these facts must not be allowed to hold up once more a thorough review of the general practitioner's claims. Apart from anything else, Mr. Marquand's first task is to secure a contented profession so that whatever other difficulties may exist doctors will tackle them with a good will and even, perhaps, with enthusiasm.

THE B_{12} GROUP OF VITAMINS

In the opening pages of this issue Dr. E. Lester Smith brings up to date the account of vitamin B_{12} which he gave in this *Journal* a little over a year ago.[1] He now reviews recent chemical and biological work on the vitamin obtained in crystalline form from the liver, and on two other closely related crystalline red substances, vitamins $B_{12}c$ and $B_{12}d$, obtained from the liquors in which the mould *Streptomyces griseus* had been grown. Partition chromatography has made the isolation of these substances possible, and differences in chromatographic behaviour have also helped in distinguishing between them—for example, between vitamin $B_{12}d$, obtained from *S. griseus*, and vitamin $B_{12}b$, another red factor obtainable from liver and similar to B_{12}. In addition, a characteristic pattern of light absorption distinguishes the B_{12} group

of pigments. Vitamin $B_{12}b$ has the same absorption spectrum as the $B_{12}d$ pigment from *S. griseus*, but the spectrum of $B_{12}c$ from the same mould is different. Differences in the form of the bacterial colonies grown are observed when these various B_{12} liver vitamins are added as microbiological growth factors to the test culture media. Dr. Smith indicates that the members of the B_{12} group probably possess small intramolecular differences, whereas the naturally occurring members of the folic-acid group differ among themselves only in the peptide side chain, especially by different degrees of polyglutamyl conjugation of the pteroylglutamic acid. A notable feature of the structure of vitamin B_{12} has recently emerged, several groups of workers showing that a cyanide group is co-ordinated with the cobalt atom. Vitamin $B_{12}b$, which is chemically more reactive, has no cyanide group, and may be identical with vitamin $B_{12}a$, obtained by the reduction of B_{12}. That the presence of the cyanide group does not confer toxicity on vitamin B_{12} was clearly demonstrated by American workers,[2] who observed no untoward effect in mice after the injection of enormous doses of the substance. The complexity of the vitamin B_{12} molecule is illustrated by the partial formula which Dr. Smith gives in his article. The largest component of the molecule of the vitamin is a red nitrogenous acid in which the cobalt is found, but which is still of unknown structure. There is recent evidence that the cobalt atom is also co-ordinated with the benziminazole ring.[3] The natural importance of amino-alcohols has long been realized in such compounds as choline, lecithin, and sphingosine, and it is interesting that 1-amino-2-propanol occurs in vitamin B_{12}.

Although it is very probable that vitamin B_{12} is not restricted to the erythropoietic tissues in its action and is required by growing tissues generally, its special functions are largely unknown. There is evidence that it is concerned with transmethylation reactions, and perhaps with the availability of sulphydryl groups. When certain micro-organisms are cultured anaerobically vitamin B_{12} is not necessary for their growth. The evidence from microbiological work in particular suggests a connexion between the actions of folic acid and vitamin B_{12} in the building-up of precursors for nucleic-acid formation. The B_{12} group may act in parallel as co-enzymes in the synthesis of pyrimidines and purines. Hardly any direct evidence exists at present linking requirements for these vitamins with special cellular processes in higher organisms, but in the case of human megaloblastic anaemias certain fundamental assumptions are receiving added support. In previous issues of this *Journal* Hall[4] and Ungley[5] have put forward evidence that vitamin B_{12} may well be the extrinsic factor of Castle, and that in pernicious anaemia in particular failure of production of the intrinsic factor is an essential feature of the disease.

Three papers in this issue discuss the clinical response to treatment with vitamins of the B_{12} group. Dr. J. N. Marshall Chalmers (page 161) reports the results of his studies on the haemopoietic action in cases of pernicious anaemia of the two crystalline *Streptomyces* vitamins, $B_{12}c$ and $B_{12}d$. Single injections of vitamin $B_{12}c$ were effective in all of nine patients treated, and similar results were obtained in the patients treated with vitamin $B_{12}d$. Haemopoietic responses were measured by the gain in erythrocytes in 15 days.[6] Dr. G. C. K. Reid (page 164) has also treated two cases of pernicious anaemia with crystalline vitamin $B_{12}d$, obtaining haematological responses to single intramuscular doses of only 10 μg. Dr. C. C. Ungley (page 152) very thoroughly investigated the responses of 24 patients with pernicious anaemia to single doses of vitamin $B_{12}c$, graded logarithmically from 10 to 160 μg. He found rather wide individual variation, similar to that observed when vitamin B_{12} is given in comparable doses. However, when mean responses to a given dose of vitamin $B_{12}c$ were compared with the mean expected response[7] from a similar dose of vitamin B_{12} the agreement was very good, and the average difference between observed and expected response exceeded the standard error of the difference in only one group, that receiving the smallest dose (10 μg.). In the whole series the most consistent responses were obtained with the fairly high doses of 40 μg. and over. Maintenance therapy was successfully carried out with fortnightly doses of 10 μg. in 20 patients, who showed no definite signs of neurological complications for periods up to nine months. Vitamin B_{12}, in doses of usually 40–80 μg. a week, was given to six patients with subacute combined degeneration of the cord and to eight with paraesthesiae; the results suggested an action similar to that of vitamin B_{12} in slowing or arresting the changes in the nervous system.

These observers all agree that their results, in so far as their patients have been followed to date, indicate close similarity in haemopoietic activity between liver vitamin B_{12} and the vitamins $B_{12}c$ and $B_{12}d$ from *Streptomyces griseus*. American work on vitamin $B_{12}b$ also indicates a like activity.[8] Apart from its relevance to the study of haemopoiesis, this similarity in action of closely related vitamins from

[1] *British Medical Journal*, 1949, **2**, 1367. See also leading article on p. 1397.
[2] Brink, N. G., *et al.*, *Science*, 1950, **112**, 354.
[3] Beaven, V., *et al.*, *J. Pharm. Pharmacol.*, 1950, **2**, 944.
[4] *British Medical Journal*, 1950, **2**, 585. See also leading article on p. 612.
[5] Ibid., 1950, **2**, 905, 908, 911 (with Childs, G. A.), and 915. See also leading article on p. 933.
[6] Della Vida, B. L., and Dyke, S. C., *Lancet*, 1942, **2**, 275.
[7] Ungley, C. C., *British Medical Journal*, 1949, **2**, 1370.
[8] Lichtman, H., *et al.*, *Proc. Soc. exp. Biol., N.Y.*, 1949, **72**, 643.

widely separated natural sources has an important bearing on the general problem of growth factors and cellular metabolism.

NEW TESTS FOR HEARING

The classification of the causes of loss of hearing have long depended on the tuning-fork tests of Weber, Rinne, and Schwabach. The introduction of pure-tone audiometry made possible a more precise assessment of the degree of hearing loss and proved of some value when used as a qualitative test. Hitherto the audiometer has been used to determine the lowest level at which the subject can hear pure tones—in other words, the threshold of hearing—by air conduction through the external auditory meatus and by bone conduction of the tone through the mastoid process. Advances in radio engineering have made it possible to calibrate the loudness of amplified speech in physical units, and the application of this new knowledge to the problems of deafness has resulted in the new test of speech audiometry. The use of pure-tone threshold audiometry to determine the hearing loss by air and bone conduction, and the relation between the hearing by air and bone conduction, offers some guide to the type of deafness. While it was often possible to place the site of deafness in either the conductive mechanism of the middle ear or in the perceptive mechanism of the cochlea and central connexions to the higher centres (so-called nerve deafness), contradictory or doubtful results were common, and later investigations often proved that earlier assumptions based on pure-tone threshold audiometry were wrong. One limitation in particular has long been apparent—namely, that while nerve deafness may be diagnosable by the old criteria it has not been possible to go further and say what particular components of the perceptive mechanism have been affected, and in what way.

Two new tests for hearing—the "loudness recruitment test" and the "intelligibility test for amplified speech"—have recently been discussed by Dix, Hallpike, and Hood.[1] The former test was devised originally by Fowler[2] and is based on the conception of the recruitment phenomenon. In a case of pure conduction deafness, when the lesion is limited to the middle ear—the scarring after infective otitis media is an example—sound entering the meatus has to pass through a defective conducting mechanism and loses an undue proportion of its energy in its passage through the middle ear. Once it reaches the organ of Corti, because it is reacting on a normal end-organ, it causes a normal, though diminished, stimulus in the auditory nerve. Increasing the loudness of the sound entering the meatus will cause a proportional increase in the stimulus in the auditory nerve. When the lesion causing the loss of hearing is confined to the organ of Corti, sound will reach the cochlea with little loss of energy, but the defective end-organ will fail to give a normal stimulus. If the intensity of the sound is low it will, as in the case of a conductive lesion, cause an abnormally weak stimulus. When the intensity of the sound entering the ear is increased it is found that the stimulus arising in the auditory tract is no longer proportional but increases at a greater rate—that is, recruitment has occurred. For example, when one ear only is deafened and exhibits the phenomenon of recruitment, the other ear being normal, at low intensities there will be a difference between the energy values of pure tones which cause a sensation of equal loudness in both ears, whereas at high intensities a sensation of equal loudness will result in both ears from sounds of equal, or nearly equal, intensity. An extreme example of this is found in the elderly deaf patient who, unable to hear a conversation when spoken in a quiet voice, will protest that he is being shouted at when the speaker raises his voice a little. The intelligibility test for amplified speech is based on the recognition that in nerve deafness, as assessed by the old criteria, inability to hear speech tends to be out of proportion to the threshold sensitivity to sound. In other words, while these patients hear the sounds of speech, their capacity to understand them is disappointingly low. With conductive deafness this disproportion between hearing and understanding is not present: if the sounds of speech can be made to reach the cochlea at all, they are in general well understood. It has come to be recognized that restoration of intelligibility—for instance, by means of hearing-aids—tends to be unsatisfactory in patients with nerve deafness but is generally very successful in patients with conduction deafness.

The validity of these beliefs was confirmed in the course of work carried out by Dix, Hallpike, and Hood on behalf of the Electro-acoustics Committee of the Medical Research Council, using the methods described in the committee's report.[3] When submitting patients to the loudness recruitment and intelligibility for amplified speech tests, they found that if the site of the lesion was in the organ of Corti, as in Ménière's disease, recruitment of loudness was the rule, but intelligibility to speech did not rise in proportion to its degree of amplification. In fact, amplification above a certain level resulted in diminished intelligibility in some cases. When the lesion was in the nerve fibrils, as in cases of auditory neuroma,

[1] *Proc. R. Soc. Med.*, 1949, **42**, 527.
[2] *Arch. Otolaryng., Chicago*, 1936, **24**, 731.
[3] *Hearing Aids and Audiometers, Spec. Rep. Ser. med. Res. Coun., Lond.*, No. 261, 1947, H.M.S.O.

recruitment of loudness was characteristically not present at all, and the intelligibility for amplified speech rose proportionally with the amplification: the type of response, in fact, was more like that found in conduction deafness. In a number of cases, however, some degree of recruitment occurred, which the authors considered to be due to degeneration of the hair cells secondary to disturbance of the cochlear blood supply by tumour pressure. Though the principles which underlie the use of these tests are still not well understood, they should prove useful in elucidating the anatomical basis of nerve deafness.

OPHTHALMOLOGISTS' FEES

When the Minister of Health cut the sight-testing fee of ophthalmic medical practitioners on April 1, 1949, from 31s. 6d. a case to 25s., an assurance[1] was given that it would be appropriately readjusted in accordance with the findings of a working party to be set up. At the time this seemed to be a reasonable assurance and was expressed as a promise that seemed likely to be kept. But, as the record of subsequent negotiations in this week's *Supplement* shows, the Ministry has made a new and even lower offer—this time of 20s.—based on different calculations. A special meeting of the Ophthalmic Group Committee of the B.M.A. is to be held on February 9, and meanwhile ophthalmic medical practitioners throughout the country will hold meetings to discuss what advice to give to their representatives.

The original fee of 31s. 6d., which was given on the supposition that the time given to a patient was half an hour on the average, was cut because the Ministry, after making some limited inquiries, believed the time to be about 24 minutes a case. The Minister then promised that "if the proposed investigation should reveal that the reduction is not fully justified an appropriate adjustment would be made in the fee subsequently fixed." The investigation was duly carried out by a working party under Mr. W. Penman and reported in March, 1950.[2] The result of it was to show that the average time, together with certain adjustments, taken in sight tests was 27.4 minutes. This conclusion was considered by the working party to be statistically sound, and the Ministry has not challenged it on those grounds, though by one minor alteration it has made the time 27.1 minutes. There is in fact a good case for saying that the average time of 30 minutes is about right, for the remaining 2.9 minutes is often taken up by patients arriving late for appointments, telephone calls, and other delays and duties not included in the working party's survey. The Minister would have been expected therefore to restore retrospectively the fee to 31s. 6d. in view of the promise he had made, or at least to 28s. 3d. to accord with the findings of the working party.

When negotiations started again the ophthalmic medical practitioners' representatives had to concede to the Ministry that there were other relevant factors besides the average time taken for sight-testing, and one of these is the remuneration received by S.H.M.O.s and consultants in the hospital service, which had not been finally fixed when the ophthalmic medical practitioners' fees were originally agreed. In other words, it was agreed that it would be anomalous if ophthalmic medical practitioners in the supplementary ophthalmic service could earn more than consultants in ophthalmology in the hospitals. Various offers were made and rejected, and finally certain factors were agreed that ought to be taken into consideration in fixing the fee. These included the time of 27.1 minutes a case and the remuneration of officers with comparable clinical responsibilities in the hospital eye service. The Ministry then offered £1, and emphasized that it could not pay a higher fee in view of the need for economy in the social services.

The dismaying result of all these negotiations is therefore that ophthalmic medical practitioners have been entirely misled by the Minister of Health on what figure their fees are to be fixed at. It might be agreed that the remuneration was initially too high in comparison with that obtainable in similar branches of medicine, yet the Minister led these practitioners to believe that any adjustment to be made would be based only on working time. When his own calculations were disproved by the working party, and his promise of readjustment was on record, ophthalmic medical practitioners expected that their fees would return to the same or nearly the same figure. Instead, an offer is made to reduce them. Practitioners will now consider whether the final offer is equitable; the committee considers it is the best that can be obtained by negotiation. The manner in which it has been arrived at leaves little cause for surprise that there is so much disquiet among doctors in the Health Service.

[1] *Supplement*, 1949, 1, 92.
[2] Ibid, 1950, 1, 75.

FALLING DIPHTHERIA MORTALITY

The mortality from diphtheria, like that from other infectious diseases of childhood, has been declining in England and Wales since the beginning of the century. It is generally accepted that the very large fall in diphtheria mortality during the past decade has been due to the immunization campaign, though some maintain that, over the last 50 years, the mortality from diphtheria is not very different from the decline in scarlet-fever mortality or the mortality from whooping-cough or measles, and there has been no immunization campaign for these diseases.

Dr. W. P. D. Logan has discussed[1] this problem and compared the mortality curve of diphtheria with the mortality curves of these other diseases. He fitted curves to the quinquennial death rates per million living at ages under 15 from 1866 to 1940 for each of the four diseases. He then extrapolated the curves to 1949. Up to 1940 the curves gave a good description of mortality from these diseases. Thereafter the mortality curve from whooping-cough in 1941–9 closely agreed with the extrapolated curve; this agreement shows that the rate of decline has not been disturbed since 1940. The

[1] *Med. Offr*, 1950, 84, 217.

mortality rates for measles after 1940 were considerably lower than the theoretical ones obtained from the extrapolated curve; in 1948 and 1949 the observed death rates of 23 and 30 per million were about half the expected values. The mortality trends of both scarlet fever and diphtheria departed considerably during 1941–9 from the expected trends given by the extrapolated curves; the observed death rates from both diseases have declined further and further below the calculated values. In 1949 the death rate from scarlet fever (1.4 per million) was only one-tenth, and the death rate from diphtheria (7.1 per million) only one-twenty-second, of the values expected from the projection of the earlier mortality trends.

But the similarity of the recent trends of scarlet fever and diphtheria was not due to similar causes. For the incidence of notified cases of scarlet fever fell by 11% between 1938–40 and 1949, while the incidence of notified cases of diphtheria fell by 91%. The fall in the death rate from scarlet fever has therefore been due to a decreased fatality rate and not to a decreased incidence, whereas the fall in the diphtheria death rate has been due to a tremendous fall in the incidence of notified cases as well as to a reduction in fatality.

In 1950 the numbers of notified cases and of deaths from diphtheria in England and Wales continued the downward trend: the numbers of notified cases in 1948, 1949, and 1950 were 7,903, 4,929, and 2,858; these numbers are 75%, 62%, and 58% of the numbers recorded in each preceding year. Deaths in the 126 great towns fell in the five years 1946–50 as follows: 258, 130, 100, 51, 27.

HOPE FOR REGISTRARS

A statement on the future of registrars which has been agreed between the Joint Committee and the Ministry of Health appears in the *Supplement* at page 24, together with a summary of the Joint Committee's views on the problem. It goes some way to allaying much of the anxiety that registrars have felt since the publication of the circular proposing to cut their numbers drastically. In particular, it states that "there is no intention of immediately displacing any registrar whose services are required by the hospital, whether in an existing appointment or as a replacement." Registrars who feared immediate dismissal will find some comfort in the assurance that the reduction in numbers—and some reduction is apparently necessary—is to be spread over at least 12 months, and the actual number of registrars needed in the hospital service is to be reviewed in the light of inquiries by medical teams throughout the country.

The Joint Committee is to be congratulated on the speed with which it has rectified what looked like being a grave administrative blunder of Mr. Bevan's. Hospital boards are now considering what establishments they require to provide adequate services in their areas, and the Joint Committee will no doubt continue to watch closely the Ministry's attitude to any proposals the boards make and to represent vigorously the needs both of the hospital services and of those who work them. The Ministry for its part has promised that it does not intend to dictate arbitrary establishments to hospital boards.

INFLUENZA IN EUROPE

The choice of influenza as the subject for discussion at the first scientific meeting of the Section of General Practice, at the Royal Society of Medicine (reported on page 186), could hardly have been more appropriate, for no section of the profession is more conscious of the presence of influenza in our midst than the general practitioner. The first news of the present epidemic came from Sweden last August: localized outbreaks were reported due to virus A prime—an antigenic variant of virus A first recognized in the U.S.A. and in Europe in 1947. Though related to virus A, it has certain characteristics which distinguish it from previously isolated A strains such as PR8. After a lull of 2–3 months influenza reappeared in Sweden in November and spread rapidly throughout the country, extending into Norway and Denmark. It made its first appearance in Great Britain in Tyneside at Christmas and shortly afterwards appeared in Northern Ireland and in Merseyside. More recently influenza has been reported from Northern Spain, Northern France, and the Low Countries, Belgium in particular. In this country the disease has reached epidemic proportions in the north-east and north-west, but, although at the time of writing there is a definite prevalence with a mounting incidence in the south, the epidemic has so far remained remarkably localized. The deaths certified from influenza in the 126 great towns of the country in the last few weeks have been 54, 102, 458, and 890 (the week ending January 13). This is a steep rise compared with any influenza epidemic since 1929. Notifications and deaths from pneumonia have also increased sharply, particularly in the north-west, though no information about the organism responsible is yet available. The clinical characteristics of the epidemic appear to be the same as in past years: the infectivity is high, but the deaths are mainly among older patients.

Virus A prime has been isolated in several areas both in this country and on the Continent. Britain has been comparatively free from influenza due to virus A since 1943. There were localized outbreaks in 1947 and in 1949; the extensive epidemic in Europe in the latter year started in Sardinia in 1948 and spread throughout the Continent from Italy to Iceland, but hardly affected this country or Scandinavia.[1] We in Great Britain looked once again with gratitude on the English Channel, but rather doubted whether the full story of our apparent immunity lay in this precious stretch of water. Much of Europe is thus experiencing its second extensive epidemic in two years and Great Britain the first for seven years.

It used to be thought that influenza travelled round the world, the disease spreading from one country to

[1] Chu, C. M., Andrewes, C. H., and Gledhill, A. W., *Bull. World Hlth Org.* 1950, 3, 187

another. The sudden appearance of influenza of the same antigenic type over a wide geographical area at the same time makes this idea of spread unlikely, though it is undoubtedly important in local extension from the primary focus. The appearance of influenza in Europe this winter at four focal points—Scandinavia, Great Britain, Northern Ireland, and Northern Spain—none of which was seriously affected by the 1949 epidemic, is of particular interest. What happens to the virus in the inter-epidemic period is another puzzling question. The World Influenza Centre at the National Institute for Medical Research has many difficult problems to tackle, but a study of the last two European epidemics may provide some of the answers to these questions. One informative report has already been published.[1]

ACETYLCHOLINE AND CARDIAC MUSCLE

The close relation between acetylcholine and the contraction of skeletal muscle became widely known as the result of the work of Dale and his colleagues[2 3] 16 years ago, when they demonstrated that the nerve impulse excited the muscle through the liberation of this substance. Recently new facts have come to light about the action of acetylcholine on cardiac muscle—an action which at first sight seems totally different from that on skeletal muscle, for acetylcholine, when liberated at vagal nerve endings or directly applied to the heart, slows the rate and diminishes the amplitude of contraction. Various workers, of whom the first was Sachs,[4] have observed that acetylcholine in low concentrations has sometimes the opposite effect, and McDowall,[5] among these, also found that in the presence of atropine acetylcholine stimulated the heart. Burn and Vane[6] observed that if the isolated auricles of the rabbit heart were exposed to the action of proguanil the contractions were gradually arrested, but they began again when acetylcholine was applied. A demonstration of the stimulant action of acetylcholine in the absence of other drugs was finally obtained by Bülbring and Burn,[7] who showed that when the isolated rabbit auricles were allowed to beat until they stopped after 24 to 30 hours the addition of acetylcholine caused them to beat again, and further additions increased the contractions until the beat was fully re-established.

Thus the existence of two actions of acetylcholine on cardiac muscle has been proved, and the contrast between the stimulant action on skeletal muscle and the inhibitory action on cardiac muscle is no longer so complete. Other observations have also helped to remove obscurities. It has been shown that the auricles of the rabbit contain an enzyme which is capable of transforming choline into acetylcholine,[8] and which is preserved when the auricles are converted to a dry powder by mincing and grinding in acetone. The amount of acetylcholine synthesized by a given weight of the powder can be measured, and this amount has been found to vary according to the activity of the auricles. When the auricles are freshly removed from the rabbit, and highly active, the amount of acetylcholine synthesized is large, but when they have ceased to beat after isolation for 30 hours the amount is small. Further, when the auricles have been stimulated by acetylcholine to resume beating, the amount of acetylcholine synthesized is again high. Addition of acetylcholine to the powder affects this process of synthesis just as it affects the activity of the contracting auricles in the bath: it depresses the power of synthesis possessed by powder made from fresh auricles and it augments that power in powder made from auricles which have ceased to beat.

These observations afford strong evidence that the contractions of auricular muscle are proportional in amplitude to the amount of acetylcholine synthesized. If this is true it seems possible that acetylcholine synthesized in the auricular tissue may be responsible for exciting the contraction in the same way as it excites the contraction in skeletal muscle when liberated by the motor nerve.

[2] *J. Physiol., Lond.*, 1936, **86**, 353.
[3] Ibid., 1936, **87**, 394.
[4] *Cardiologia, Basel*, 1937, **1**, 74.
[5] *J. Physiol., Lond.*, 1946, **104**, 392.
[6] Ibid., 1949, **108**, 104.
[7] Ibid., 1949, **108**, 508.
[8] Comline, R. S., ibid., 1946, **105**, 6P.

MAN-EATING SHARKS

Records of shark attacks in Australian waters date back to 1793, and in an interesting paper Coppleson[1] has reviewed the accounts published during the past 30 years. Four to five attacks on an average are reported annually around the Australian coast, half of these being in pearl divers, the remainder in pleasure bathers. More than half of the attacks on bathers are made in the surf, most of the rest in rivers or harbours, but a few in the open sea. The old myth that sharks do not attack dead bodies has been completely exploded, and stories about their digestive powers have also proved unfounded. Well-recognizable limbs have been recovered from the achlorhydric shark's stomach several weeks after ingestion. Not unnaturally the attacks mostly occur in the warm months of the year—between November and April. The great majority of the incidents are in the afternoon hours, between 3 and 6 o'clock, and it is usually the solitary bather who is attacked either in deep or shallow water. There appears to be no common factor in weather, tide, or type of water. Wounds caused by sharks vary from amputation of a limb (a femur can be cleanly bitten through) to abrasions. The latter are usually due to the shark's rough hide, while the fin can readily cause deep lacerations. Of the last 74 cases reported, 51 of the victims have died. All but seven of these reached or were brought to the shore. There are many varieties of sharks found around the Australian coast—35 species have been identified off the New South Wales coast alone—but probably not more than three of these have been definitely proved to be "man-eaters"—the white shark, the whaler, and the tiger. Coppleson discusses the value of "meshing" as a prophylactic method, and he points out in conclusion that though the injuries concerned are indeed horrible, and occur mainly in a healthy group of the population, the risks to the individual bather are minimal.

[1] *Med. J. Aust.*, 1950, **2**, 680.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

SCARLET FEVER

BY

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During the past few years, when scarlet fever has ceased to be an important cause of death or of serious morbidity, it has become conventional to regard the disease as of little consequence and to dismiss the apparatus of notification and hospital isolation, still widely practised, as a waste of time and resources. This has not resulted from any lack of appreciation of the importance of streptococcal infections, but rather from an awareness of the pathological potential of all such infections, so that paradoxically there has arisen a tendency to exalt the importance of almost all streptococcal infections except scarlet fever, and to dismiss the latter as merely differing from streptococcal tonsillitis in that a rash is present.

Epidemiologically, of course, there is no difference, and, from the standpoint of practical affairs, it is regrettable that in the past there has been too much emphasis on scarlet fever to the exclusion of other streptococcal infections, but is it rational to dismiss the rash so lightly? After all, it is the physical expression of a generalized toxaemia, which, added to the dangerous possibilities of a streptococcal invasion of the respiratory tract, cannot diminish in any way the sum total of the disease process. Again, while we may be thankful that at present scarlet fever is a mild infection we must remember that this was not always so, and Greenwood has pointed out that "scarlet fever is the most beautiful example within the range of epidemiology—an even more striking example than that of smallpox—of change of type, a change which has been effected certainly twice and probably three times in this country within the limits of modern history."

We are quite in the dark about the factor or factors which have operated to bring about these changes. It is tempting to look to our relatively superior environmental and economic conditions as accounting for our present favourable experience, but this cannot be the whole story, as in the first 25 years of the nineteenth century scarlet fever also showed itself in mild epidemic form, although this was a period in which conditions were economically very bad. In view of past history, therefore, and in the absence of knowledge of the factors determining major epidemiological changes, he would be bold who would predict that severe scarlet fever will never occur again. However, in such an event we shall be in possession of remedies much more potent than in the past to deal with the situation.

Definition

It has also been questioned whether the term "scarlet fever" has any claim to be retained in the clinician's vocabulary, and whether it would not be better to refer to all forms of streptococcal infection by some such designation as streptococcal fever. In my view this would result in some loss of precision, and, so long as we realize that scarlet fever can no longer be regarded as an epidemiological entity, there is no reason why we should not continue to use the term as a convenient description for a well-recognized combination of signs and symptoms which repeats itself often enough to be regarded as a clinical entity. This need not prevent us from recognizing that, as in most other diseases, from time to time one or other common feature may be absent in individual cases, thus to some extent altering the clinical picture.

For practical purposes, therefore, we would define scarlet fever as one of the clinical manifestations of streptococcal infection characterized in the acute febrile stage by faucial inflammation and a generalized erythematous rash, and later by the occurrence of desquamation and of certain complications such as acute otitis media and adenitis caused by lymphatic spread of the streptococcus, and by others such as arthritis occurring at the end of the first week and nephritis which appears at about the end of the third week after onset and the aetiology of which is still undetermined.

Aetiology

To give a reasonable account of present-day views on scarlet fever we must go back to the investigations of the Dicks in 1923 and Dochez in 1924. Their work pointed almost conclusively to the haemolytic streptococcus as the causal organism of the disease, and, although well-marked biological differences were later found to occur within the group roughly defined by this term, no specific relationship could be shown to exist between any particular strain and scarlet fever. Thus Lancefield in 1933, by a precipitation method, showed that streptococci from most cases of scarlet fever fell within Group A, which, however, contained streptococci from many other forms of human streptococcal infection.

Again, by specific agglutination reactions, Griffith in 1935 subdivided the streptococci responsible for human disease into about 40 serological types and regarded these as constituting a bacterial species which he named *Streptococcus pyogenes*. His method of typing, when applied to tracing the spread of streptococcal infection among members of a community, indicated that such common clinical conditions as scarlet fever, streptococcal sore throat, erysipelas, and puerperal sepsis might be caused by the same serological strain, and in view of these findings epidemiologists had to recast their ideas on the subject of scarlet fever. The disease could no longer be regarded as forming an epidemiological entity in the sense that a patent infection derived from a case of scarlet fever would necessarily be another case of scarlet fever; it could be regarded only as one clinical manifestation of epidemic streptococcal disease which might result in a variety of clinical forms to each of which the clinician, for descriptive purposes, might apply a separate term.

Pathology

The discovery of the haemolytic streptococcus as the cause of scarlet fever also provided a basis for the present-day conception of the pathogenesis of the disease. The streptococcus is now regarded as having two main pathological activities—a pyogenic and a toxigenic. When recognizable infection occurs pyogenic activities produce inflammation at the site of implantation, usually the fauces and nasopharynx, while as a result of the toxin-producing activities an exotoxin is liberated into the blood stream and causes a general toxaemia which shows itself by the occurrence of the erythematous rash.

At any stage from the earliest part of the acute eruptive phase until convalescence is well advanced the pyogenic properties of the organism may display themselves and by lymphatic spread set up such septic complications as acute otitis media and cervical adenitis. To account for such complications as rheumatism and nephritis, complications which may follow all streptococcal infections of the upper respiratory tract, various explanations have been advanced, some believing that they may be the result of sensitization following infection, and others ascribing them to the release of, as yet, undifferentiated toxins. So far as pyogenic complications are concerned, however, this is not the whole story, as these, especially in the multiple-bedded wards of hospitals, may not be the pathological expression of the activities of the original invading organism.

Allison and Brown in 1937, employing the method of typing introduced by Griffith, found that when complications occurred in patients treated in large wards, at the time of development of the complication the streptococcus isolated was often of a serological type differing from that grown at the onset of the attack of scarlet fever. From this they concluded that, as a large ward was likely to contain patients with a variety of serological types of streptococcus, complications resulted from the interchange of organisms which was found to occur in such a community. This, of course, would imply a very narrow specificity in the immunity resulting from infection by individual types. With regard to antitoxic immunity acquired from exposure to the soluble exotoxin, or erythrotoxin as it is often called owing to its property of evoking the scarlatinal rash, although it has been suggested that there are certain differences within the group of erythrogenic toxins, practical experience shows that these cannot be great, if they exist at all.

Dick and Schultz–Charlton Reactions

Two immunity reactions in the human subject are described in connexion with scarlet fever—the Dick and the Schultz–Charlton tests. It may be thought that a consideration of these is somewhat academic, but for completeness a brief account of each is given.

The Dick test for susceptibility to scarlet fever is performed by the intradermal injection of 0.2 ml. of a suitable dilution of scarlet-fever toxin, which is the filtrate derived from a broth culture of a strain of haemolytic streptococcus known to be a good toxin producer. It is usually carried out on the flexor surface of the left forearm and controlled in the other arm by a similar injection of toxin which has been inactivated by heat. In susceptibles a circumscribed patch of erythema, 10–40 mm. in diameter, appears from six hours onwards and reaches its maximum intensity in 18 to 24 hours. In immunes no reaction occurs at the site of injection. Pseudo-reactions due to the non-specific constituents of the test material are not numerous.

The test has given interesting results when performed on a large scale in the general population, positive reactors appearing from the fifth to sixth month of life onwards, reaching a maximum of 70 to 80% in the first and second years, and thereafter declining into adult life, approximately 20% being Dick-positive at the age of 20. Theoretically the Dick test should be of assistance in diagnosis, as all cases should be Dick-positive in the earliest stages, and a reversal to negative during convalescence would be absolute confirmation of the diagnosis. In practice, however, the value of the test in diagnosis is limited by the fact that all cases of scarlet fever do not give a positive result in the early stages, and a fair proportion remain positive throughout convalescence. At the present time the main application of the test is in deciding whether active immunization should be conferred on persons exposed to special risk of scarlet fever—for example, entrants to the nursing service of fever hospitals.

The Schultz–Charlton test, often described as the blanching or extinction phenomenon, is performed by the intradermal injection of 0.2 ml. of diluted scarlet-fever antitoxin into an area of skin where the rash is well marked—for example, on the abdomen. In the great majority of rashes in the early stage a localized disappearance of the rash is found over the area of skin infiltrated by the serum in from 6 to 18 hours after performing the test. The reaction is very convincing usually and is specific for scarlet fever; as it is relatively easy to perform, it might be held to be valuable in diagnosis, but in practice there are definite limits to its usefulness. For example, it is best seen in typical rashes in which little assistance in diagnosis is required. On the other hand, in later faded rashes, in faint transient rashes, or in coarse equivocal rashes the results are often disappointing, and even in hospital the test is not much employed nowadays.

It might be mentioned here that for diagnosis in difficult cases throat swabs examined for the presence of haemolytic streptococci are useful, not so much from the point of view of confirming the diagnosis as for their value in excluding the diagnosis of scarlet fever. One or two negative cultures for the haemolytic streptococcus obtained within the first few days of a febrile illness would be very strong presumptive evidence that the condition was not scarlet fever.

Treatment

Home Isolation

In past times, when a high proportion of cases of scarlet fever were isolated in hospital, the main interest of the practitioner was in diagnosis, but over a period of years several factors have combined to make the home isolation of cases of the disease a procedure to be encouraged where circumstances are satisfactory. In the prevalent mild epidemic type, severe cases are unusual and hospital authorities are only too anxious to reserve their diminished number of beds for more severe forms of infectious disease; it has been realized for years that hospital isolation of cases has done little to reduce the general incidence of scarlet fever; and, finally, what has been said about the pathogenesis of complications is a strong argument in favour of retaining

the patient in isolation in his own home. The fact also that we have potent specific remedies, the administration of which calls for only the simplest technical resources, makes the disease one which can be satisfactorily handled by the practitioner.

The patient must have a room to himself, and the following should be set apart for his exclusive use: crockery and cutlery, toilet requirements such as soap, towels, toothbrush, and hairbrush, a thermometer, and a supply of old books and toys which can be burnt afterwards. In the room an overall should be provided, and, near the door, a wash-hand basin with soap, nail-brush, and some dilute disinfectant for the hands if desired. Simple masks consisting of a few thicknesses of gauze, fixed by tapes over the mouth and nose, are also essential. The nurse and medical attendant must always put on a mask and overall when entering the room, and before leaving they should place the mask apart so that it can be included in the next batch of domestic washing, remove the overall, and scrub the hands with soap and water. Articles used in treatment or nursing should be sterilized at once—for example, crockery should be boiled or scalded after food. Rags or paper handkerchiefs should be provided to receive nasal or other discharges and burnt at once. After excreta have been deposited in the water-closet, chamber pots should be wiped out with a black fluid disinfectant. Bed and body linen can be dealt with in the domestic wash tub, and in this connexion it should be remembered that they must not on any account be sent to a public laundry.

General Management

The period of isolation recommended by various authorities for uncomplicated cases varies from two to four weeks; I now adopt a period of three weeks in hospital work, and practical experience teaches that clinical recovery from infection is a safe guide for the termination of isolation. That clinical recovery has been established presupposes a conscientious examination of the upper respiratory tract, and patients with catarrhal or suppurative discharges, even in minor form, should remain in isolation until these have cleared up. If these prove intractable admission to the isolation hospital should be sought so that specialist ear and throat attention may be directed to the eradication of the underlying pathological condition. Bacteriological standards of freedom from infectivity, unless exceptional circumstances call for them, are not generally recommended.

Mild cases should be kept in bed for seven to ten days, but in sharper attacks the patient may need to remain in bed for two to three weeks. During the acute stage the diet should be fluid, although many patients can take a light diet from the beginning, and when the temperature has fallen a full mixed diet should be given. In the early stages headache and restlessness are usually controlled by aspirin. Routine testing of the urine is wise, especially in the third week of illness, and the practitioner should not overlook routine examination of the heart.

Specific Treatment

Under this heading we must consider the sulphonamides, penicillin, and scarlet-fever antitoxin. The results of the administration of sulphonamides have been unspectacular, if not disappointing, and it is doubtful if there are many who employ these drugs in scarlet fever, especially since penicillin became available.

The action of penicillin is directly on the streptococcus, and daily bacteriological examination of throat and nose swabs for haemolytic streptococci during the course of its administration indicates that the organism disappears from cultures from the third to the fifth day of treatment. Clinically this is paralleled by the subsidence of signs and symptoms of throat inflammation. The specific toxaemia is apparently unaffected and the temperature may not come down for two or three days, whilst the rash pursues its usual course. Although it is unlikely that the streptococcus is completely eliminated, the advantage of reducing the numbers of the organism is obvious and the possibility of complications substantially minimized. When penicillin is used in the treatment of such complications as cervical adenitis, acute otitis media, and rhinitis the clinical evidence of benefit is striking. This is especially the case with otitis media, in which the further complication of mastoiditis is now almost unknown.

The effects of the injection of scarlet-fever antitoxin in the early eruptive phase of scarlet fever are well marked and consistent. The temperature is brought down by crisis in 12 to 24 hours, the rash fades early, and subjective improvement of the patient's general condition is rapidly obtained. Subsequent desquamation may be scanty or retarded in appearance, and in some cases suppressed. Antitoxin treatment, however, is no complete answer to the problem of complications, and, as the disease at present retains its importance mainly on account of these, this somewhat limits the value of the treatment.

The practical recommendation which follows from this very brief summary of the action of penicillin and scarlet-fever antitoxin is that we are prepared to advocate the administration of penicillin to all, or practically all, cases of scarlet fever at the onset of illness. It is our practice to give injections of 100,000 or 200,000 units of penicillin in aqueous solution twice daily, or an injection of the equivalent total dose of procaine penicillin once daily, the treatment being continued for five days. Complications such as acute otitis media, adenitis, rhinitis, and other respiratory infections occurring in the course of the illness require penicillin treatment on the same lines. When the initial toxaemia is sharp, as shown by a temperature of 102° F. (38.9° C.) or over and a bright rash, it is wise to employ antitoxin treatment in addition. One injection of 3,000 to 6,000 U.S.A. units of scarlet-fever antitoxin given intramuscularly at the start of treatment will usually give the required result. Obviously only a minority of cases of the present mild epidemic type of scarlet fever will require antitoxin as well as penicillin treatment.

As on all occasions on which therapeutic sera are administered, the practitioner should be on the look-out for serum sickness which I have thought to be rather more prevalent over the last year or two than in the past after injections of scarlet fever antitoxin. The common form of serum sickness after intramuscular injection is that occurring at an interval of 7–10 days after injection and which is shown by pyrexia, urticarial rash, and, occasionally, by localized oedema of the face and extremities. Should this be troublesome an injection of 1 ml. of adrenaline, 1 in 1,000, followed by a course of one of the antihistamine drugs for two or three days should relieve the patient. Before deciding to give antitoxin the practitioner should inquire into

the history of previous serum injections or such conditions as asthma or hay-fever. If there is evidence of these the practitioner would probably be content to rely on the action of penicillin alone.

Nephritis is a relatively rare complication at present, and when it occurs is much less formidable than formerly. It usually yields to dietetic restriction and alkalis. The occasional patient who develops rheumatic carditis should be carefully watched, and strict rest in bed controlled by blood sedimentation estimations and pulse recordings should be insisted on until these are satisfactory.

ASSEMBLY OF POLISH DOCTORS

The Assembly of Polish Doctors in Great Britain held a meeting in London, at the British Medical Association House, on January 19 and 20. The large attendance included Polish medical men and women from other Western countries. It was the first such meeting since the end of the war, and much fraternal feeling was manifest. The inaugural meeting was presided over by Dr. GEORGE DE SWIET, honorary president of the Polish Medical Association in Great Britain, who welcomed the company in their own language. The Poles, he said, had desired to combine a patriotic rally with some profitable scientific instruction, and had been grateful for this opportunity to come together and exchange views. Many Poles present on that occasion, like their British friends, had been combatants, and, having formed some very warm friendships on the battlefields of Europe and beyond, had felt that they would like to meet again.

Dr. de Swiet went on to thank the British Medical Association and its staff, both medical and non-medical, for the great sympathy and good will it had shown to Polish doctors who had come over to this country at a critical time in their lives. The Poles had felt the need for forming some kind of organization, and in this they had been greatly assisted by the B.M.A. He added that it was 40 years since he himself came to this hospitable country of Great Britain, and it had been his great endeavour to bring the British and Polish peoples together.

Polish Doctors in Britain

General W. ANDERS, who was commander-in-chief of the Polish Forces in the Middle East, paid a high tribute to the work done by the Polish Medical Corps during the war, in particular their treatment of malaria in Russia and their surgical work in Italy. It was stated that there were in Great Britain about 860 doctors of Polish origin and nationality, of whom some 700 had succeeded in finding a settled livelihood. The total number of Poles in this country was reckoned at some 140,000. Some further figures were given by Dr. E. L. STURDEE, who brought the greetings of the Ministry of Health. He said that about 600 Polish doctors now in this country had obtained their medical degrees in Poland before the war, and a small group had qualified in other European universities. There remained nearly 300 who had been trained in this country. He mentioned in particular the difficulties of those who were well on in middle age at the time of their exile and of those who had been specialists in Poland and could not easily find an opening for their specialty in the country in which they had taken refuge.

Dr. G. GREY TURNER, Assistant Secretary of the British Medical Association, spoke a welcome on behalf of that body. He was introduced as one who had fought side by side with the Poles at Monte Cassino, and he recalled the thrilling day when the pink and white flag of Poland was seen flying on the monastery which had for so many weeks menaced their lives. He conceived a great admiration and affection for the gallant Poles. He was also full of admiration for the way in which Polish doctors, some of them relatively advanced in age, had learned a difficult language and adapted themselves to new conditions of life and practice. He had had the pleasure of meeting a number of Polish doctors working in the Colonies, and there, too, most of them had settled down quite well and found satisfying employment. Dr. L. KOCSIS, a Hungarian doctor, offered a welcome on behalf of friendly Continental doctors. He hoped that in due time they would be able to pass on to their respective peoples the knowledge they had accumulated in exile.

Sir Alexander Fleming on Antibiotics

Sir ALEXANDER FLEMING then gave a brief address on "The Search for Antibiotics." Antibiotics, he said, were not a passing phase, they were here to stay. It could be said that their history started with penicillin; all the other antibiotics had been worked out in much the same way. The first discovery was made by the biologist; then came the chemist, who concentrated the material, purified it as far as he could, and synthesized it if possible; then the pharmacologist, who investigated its properties, in particular its toxicity, and how it was absorbed; and after him the physician came into the picture and assessed its therapeutic effect. The pharmaceutical manufacturer had to make the material in quantity, which might be the most difficult thing of all, though it was now not quite such a commercial hazard with the newer antibiotics as it had been with penicillin.

One recent development in the antibiotic field was not purely medical. It had been found that if certain of these substances were administered to chicks or young pigs there was a great enhancement of growth.

On the following day the Assembly met for a clinical session under the chairmanship of Dr. W. TOMASZEWSKI, when addresses were given by Professor Alexander Haddow, the director of the Chester Beatty Research Institute, on "Latest Results of Cancer Research," and by Dr. F. A. H. Simmonds, physician and medical director, Clare Hall Hospital, South Mimms, Herts, on "Modern Aspects of the Treatment of Pulmonary Tuberculosis." These were followed by papers in Polish, one by Dr. M. ZALESKI on radiotherapy in cancer, and another by Dr. I. M. SPITZER on the treatment of tuberculous meningitis in the adult.

Cancer Research

Professor A. HADDOW, whose address was to some extent a repetition of one which he gave recently at the Royal Institution (reported in the *British Medical Journal*, December 2, 1950, p. 1271), spoke of the remarkable progress achieved in cancer research during the last 10 years. One of the main difficulties facing the investigator was that the change from the normal to the malignant type of cell was probably due to very subtle transformations, unaccompanied by any gross alterations in the protein structure of the cell or in its immunological properties; hence there was probably no protective reaction on the part of the host, such as was found in bacterial and other infections. Yet another difficulty was that the malignant cell was probably very stable. In the chemotherapy of malignant disease they were expected to undo what amounted almost to a natural process.

He then passed in review the endocrine treatments proposed for various forms of cancer, stating that, apart from stilboestrol in prostatic cancer, these still remained of limited use. He spoke also of the action of urethane, which was characterized by a high degree of chemical specificity. A great deal of attention had been paid to nitrogen mustards, the damaging effects of which on normal tissues had long been recognized. It was not unreasonable to expect to increase the therapeutic effect of these substances by chemical modification, and during the last three years about 250 new types had been synthesized and tested biologically, and some of them clinically as well. Remissions had been obtained in cases of Hodgkin's disease and chronic lymphatic

leukaemia. The ideal chemotherapeutic agent, said Professor Haddow, would have far more specific properties than any so far examined.

At the close of his address Professor Haddow was asked his opinion about the remedy recently put forward in an article in *Picture Post*. He replied that he was out of the country at the time and actually had not read the article, but he had known of the matter. He believed that the nature of this cure offered for cancer had not been divulged; it was most likely to be a caustic of some kind. It was entirely proper that all these things should be examined, as was being done in this case, and it would be wrong to give a final opinion before the evidence was available.

Treatment of Pulmonary Tuberculosis

Dr. F. A. H. SIMMONDS then discussed before the Assembly some modern aspects of the treatment of pulmonary tuberculosis. The present time, he said, was one of rapid change; a constant reassessment had to be made of new methods of treatment, and a plain case must be stated for the scope and merits of chemotherapy. It should not be judged by itself; chemotherapy opened the way to effective surgical intervention. Indeed, in the management of pulmonary tuberculosis one could hardly speak of a specific method of treatment; all treatments had to be integrated and to be considered as complementing one another.

Bed-rest had long been accepted as fundamental. During the last few years interest in treatment by rest had stimulated the further use of this principle. Sometimes it was combined with postural treatment, particularly in unilateral cases. Various hypotheses had been brought forward to explain its benefits, but the method was sometimes helpful in cases refractory to more active methods.

Streptomycin had been shown to be a potent weapon against tuberculosis, but here again its place in treatment was still unresolved. That there were few patients who might not benefit from this agent was certain, but the questions of how to give it, how much to give, and for how long remained. Tuberculous cavities became smaller, and might even close under treatment by chemotherapy. The agent could best reach those lesions which were not too large and into which it could diffuse well; preferably there should be little or no caseation; such conditions were found in early miliary tuberculosis. In this country chemotherapy in pulmonary tuberculosis meant practically streptomycin plus *para*-aminosalicylic acid. When P.A.S. was used, strains resistant to streptomycin were less likely to be found.

Dr. Simmonds reviewed collapse therapy and other procedures, and gave particulars of the treatment of some 500 patients at Clare Hall Hospital in 1950. The more they could employ collapse therapy the better were the survival rates.

A plenary meeting of the Assembly was held under the chairmanship of Dr. S. SIKORA for the discussion of medico-social problems, when an address was given by Dr. L. SURZYNSKI on the problems facing emigré Polish doctors. The closing session was again presided over by Dr. de SWIET, and the final event was the celebration of a Mass at Brompton Oratory for the repose of those Polish doctors who fell in the war.

Breaking up bacterial cells in order to study the enzymes, bacteriophage, etc., within them has always been something of a problem, since they are small and tough. Mechanical shaking, grinding, and vibratory techniques are liable to heat the cells unduly and so destroy the fragments it is desired to study. Now Dean Fraser (in *Nature*, January 6, p. 33) has described the use of explosive decompression. The bacteria are compressed under nitrous oxide or other inert gas at a pressure of 500 lb./sq. in., and then suddenly tipped out into the open air. The sudden release of pressure bursts the cells, probably through the forceful expansion of intracellular gas.

NEW MINISTER OF HEALTH

Mr. H. A. Marquand was appointed Minister of Health on January 17 in succession to Mr. Aneurin Bevan, who became Minister of Labour and National Service. Mr. Marquand had been Minister of Pensions since July, 1948.

Responsibility for the Health Service in Scotland, where it comes under the Secretary of State, is not affected by these new arrangements.

Mr. Marquand is aged 49. Educated at Cardiff High School and the University College of Cardiff, he took the B.A. of the University of Wales with first-class honours in history in 1923, and first-class honours in economics in 1924. In 1928 he became M.A., and he took the D.Sc. in 1938. Before entering politics he was professor of industrial relations at the University College, Cardiff, and in 1926–30 he had been lecturer in economics at Birmingham University. As a lecturer he has paid several visit to the U.S.A., and he spent a year there in 1932–3 studying industrial relations. He must be the only member of the Government who is an honorary member of the American college fraternity Phi Beta Kappa. A member of the Labour Party since 1920, Mr. Marquand first entered Parliament in 1945 as Labour member for Cardiff (East). His constituency disappeared when the seats were redistributed, and he was re-elected in February, 1950, as member for Middlesbrough (East). From 1945 to 1947 he was Secretary for Overseas Trade, and then Paymaster-General for a year before being appointed Minister of Pensions. As Minister of Health he will have Cabinet rank, though not be a member of the Cabinet, and his salary will be £5,000 a year.

[Walter Stoneman, London

Reports of Societies

ROYAL SOCIETY OF MEDICINE

The presidential address to the Section of Proctology of the Royal Society of Medicine was given on January 10 by Sir Heneage Ogilvie. His subject was the large bowel and its function, and the Section was treated to a most entertaining discourse.

The Expanding Rectum

Sir HENEAGE said that this was an appropriate occasion to forget the operations of proctology and to return to a general consideration of a subject which was the foundation of this specialty. He said that a fundamental property of the rectum was its power to expand, and this was a property which it seemed to impart to its devotees. Proctologists had long since expanded their specialty far beyond its strictly anatomical boundaries: did the election of a general surgeon as their president imply that they intended to make the diaphragm their limit? And why not? The diaphragm, after all, was the most important muscle of defaecation.

Sir Heneage went on to compare and contrast the feeding habits of different species, and then discussed the form and function of the large bowel in the carnivora and herbivora. He specially emphasized the dangers of too facile

application to the human being of the results of experimental gastro-intestinal work in animals. After referring to the omnivorous habits of man, he traced the course and fate of the colonic contents with particular reference to their final storage and the act of defaecation. Once again he contrasted the behaviour of Homo sapiens with that of other creatures. The presence of abundant nourishment in the faeces of herbivora was a matter of some interest, and the baby Koala bear's ingestion of its mother's faeces and the rabbit's ingestion of its protein-containing "night faeces" were described. The methods by which animals disposed of their faeces were also of some interest, from the dik-dik, which made ineffectual attempts at burial, to the rhinoceros, which might favour a communal midden but then kicked its faeces all over the place. Various animals used excretion as a means of communication.

Man and His Faeces

Sir Heneage then described man's reaction to his own faeces, referring to the habits of Asiatic tribes, Africans, Ancient Britons, and our more recent forebears. Enemas were undoubtedly the oldest therapeutic device in the world, and Sir Heneage illustrated this by a number of remarkable pictures depicting the use of cows' horns and hollow reeds for their administration. He also depicted the oral insufflation of herbal concoctions into the rectum by medicine men, the fashionable use of the enema in the reign of Louis XIV, and its common appearance in cartoons of that period as well as in the earlier editions of Molière's *Le Malade Imaginaire*.

The development of the modern colon neurosis, the frequency of ritual self-purgation, the popularity of colon parlours, and the one-time practice of colectomy for large-bowel stasis were then discussed by Sir Heneage. He outlined the more rational outlook of the medical profession to the problem of constipation to-day, and emphasized that, while we preferred to leave things to Mother Nature, it was possible that we had overdone our negation of former beliefs. The part played in defaecation by the voluntary and involuntary muscles, and the reciprocal innervation of the rectum and its sphincters, were next discussed. Sir Heneage described the external sphincter as "this remarkable muscle, the sentinel of social security."

Summarizing the practical implications of his address, Sir Heneage said that we must wage unceasing war on coprophobia. While normal defaecation was an essential contribution to health and happiness, abnormal defaecation through a normal aperture could be a fate far worse than a well-regulated colostomy. He concluded by saying that proctologists might translate the old adage "Mens sana in corpore sano" into "Normal defaecation brings a contented mind"; likewise normal defaecation, in its own turn, came from equanimity and common sense.

INFLUENZA

A meeting of the Section of General Practice of the Royal Society of Medicine was held on January 17 for a discussion on "Influenza." Dr. G. F. ABERCROMBIE presided.

Dr. E. P. SCOTT defined influenza as an acute disease of doubtful aetiology, characterized by fever, prostration, and great liability to pulmonary complications, and of epidemic incidence. The course of influenza was unpredictable. In a hefty young person the disease might proceed to a fatal issue, while an elderly person, with a poor "life," in the same house, might be laid up only for two or three days. Early diagnosis was of great importance; by far the most sinister aspect of influenza was its liability to mask some chronic or intercurrent disease. He recalled a case of carcinoma of the lung which had been diagnosed in its initial phase over a considerable period as influenza. In the war he recalled how one young medical officer diagnosed as influenza a case of cerebrospinal meningitis, with disastrous results. If a case of supposed influenza did not begin to clear up after three or four days on the usual remedies, or if vomiting occurred, it signified some more serious condition. Dr. Scott believed that penicillin was too widely used in the initial stages of influenza, in many cases at the request of the patient himself; its injudicious use caused penicillin-resistant organisms to be spread among the community. Sulphonamides he used frequently, and salicylates were still helpful. In influenza convalescence was prolonged often out of all proportion to the severity of the attack.

Pattern of Previous Pandemics

Sir HORACE EVANS said that there had been eight great pandemics since the beginning of the sixteenth century, and most of them had occurred in three waves, the first involving large populations but relatively mild in attack, and the second and third being less extensive but more severe. The spread of the disease might be so rapid that within a few hours a whole household was laid low. The onset was sudden, with fever, headache, shivering, muscular pains, and prostration, and in some cases there might be marked photophobia and typical abdominal pain. In most cases pulse and respiration rates were quickened. Fever in uncomplicated cases persisted for about four days and was usually remittent. By the second or third day bronchopneumonic complications might dominate the picture. Post-influenzal depression was well known.

The mild or moderate case of influenza might be confused with a number of other maladies, but most commonly with the common cold or with febrile catarrh. Among other conditions which might be confused with mild influenza he mentioned poliomyelitis, encephalitis, measles, whooping-cough, and enteric fever—all febrile illnesses frequently accompanied by catarrh in their early phase. Another group of conditions, possibly of virus origin, which might give rise to difficulty were glandular fever, infective hepatitis, and what was sometimes called atypical pneumonia. In most of these, in contrast to influenza, the onset was insidious.

Diagnosis

Dr. C. H. ANDREWES said that influenza virus A was one of the viruses about which they knew most; he himself had been working on it for 18 years. It was possible to distinguish between true influenza due to virus A or B and those febrile catarrhs with which it was most easy to confuse it. The distinction could be made epidemiologically and clinically, as well as in the laboratory, though not with any great certainty. The late Dr. Major Greenwood used to say that the distinction between a cold and influenza was the same as between crows and rooks—if one saw one or two birds they were crows, if a whole lot they were rooks.

He agreed entirely with Sir Horace Evans in holding that influenza was distinguished by the sudden onset, when the respiratory symptoms were much less evident than the general symptoms. But it was very difficult indeed for the practitioner, seeing the odd case, to say whether it was due to influenza or to febrile catarrh. In the laboratory the disease could be diagnosed pretty certainly either by the recovery of the virus or by serological or complement-fixation tests, but this was not of much use to the clinician, because the tests could not be done quickly enough to help him.

"Gastric 'Flu"

He thought there were very strong grounds for disbelief in what was called "gastric 'flu." He had examined many cases of supposed gastro-intestinal influenza, but had found no evidence that they had anything to do with the influenza virus.

Dr. Andrewes believed that the general practitioner could add to knowledge about influenza if he would study the small epidemics which might be influenza and report them to the National Institute for Medical Research at Mill Hill or to the Ministry of Health, where they could be followed

up. In particular some clue might be given about what happened to influenza between the little outbreaks in the early summer and in the late autumn.

The Present Epidemic

In the course of some general discussion Dr. J. D. SIMPSON said that it was accepted that an influenza epidemic occurred in two or three waves. During the first wave the disease tended to attack the young and the old, and it took an extremely virulent form such as, he understood, occurred in the 1914–18 war, when many young people succumbed to a pneumonia in the course of 24–48 hours. It appeared that, in the pattern of the epidemic which was being experienced at the moment, the very young were exempt, but in the old there was a ready development of pulmonary complications. This was a justification for the exhibition of sulphonamides and antibiotics, not as a treatment of pneumonia but to protect patients from the pneumonia which so commonly developed.

Dr. J. FRY said that out of 130 cases of influenza which he had seen during the last three weeks, about 17 had developed what appeared to be a mild basal pneumonia. The youngest of these patients was 9, but most of them were over 50, the oldest being 78. The usual course was three to four days, the temperature falling at about the fourth day, but the cough persisted. There was no response to any of the antibiotics.

Dr. G. O. BARBER said that it had been impressed upon them that influenza was a disease due to a specific virus—it was essentially a toxaemia, and the symptoms of toxaemia were observed in the patients. The virus had the characteristic, however, of lowering the resistance to secondary invaders, and so there might be also a whole range of symptoms due to such invasion. It was useful to distinguish between the essential toxaemia of the virus and the effect of the invasion by other organisms. In the differential diagnosis of early influenza it was from other virus toxaemias that it was most difficult to differentiate during the first twenty-four hours, apart from the acuteness of onset. He disagreed with one speaker who had said that the headache was always due to sinusitis; that might be so in the secondary stage, but not during the toxaemic stage. He agreed that it was rare in the present epidemic to find very young children attacked—he did not think he had seen any under the age of 5. Nor in this epidemic had he seen many instances in which the whole family had gone down; it was more frequent to find ones or twos attacked. Dr. DAVIES referred to another characteristic of the present epidemic, that the people who were getting the disease were those who had not troubled the doctor for perhaps ten years.

Dr. BEAUMONT recalled the influenza epidemic of 1918; it had been characterized by haemorrhagic lesions in the lungs, and many of the patients had acute abdominal pain. It seemed rather difficult to suppose that a patient who had all the features of respiratory influenza should, when he developed abdominal signs and symptoms, be suffering from another disease at the same time. Dr. ANDREWES said that his point was that epidemics which were predominantly gastro-intestinal in character were most unlikely to be influenza. He added that he wished that some balance could be observed in the Press in reporting influenza outbreaks. Just before he left home he learned that a message had been received from the United States asking what steps were being taken to restrict travel from Great Britain to America in view of the influenza situation.

Dr. MILNER, Dr. DELISLE GRAY, Dr. GRAHAM, and others continued the discussion.

Lord WEBB-JOHNSON, President of the Society, said that perhaps the most important point which had emerged during the discussion concerned bias in clinical medicine. Especially in times of epidemic was it important to be aware of such bias in oneself and others. There was another bias which affected not general practitioners but specialists, particularly those who specialized in a very narrow field. It was the bias favouring the view that the abnormal condition belonged to their own specialty.

Nova et Vetera

HISTORICAL ESSAYS

Essays in the History of Medicine. By George Gask. (Pp 210. 30s.) London: Butterworth. 1950.

During his active career Professor Gask (whose death is recorded with regret on another page) exercised a very wide influence on the development of surgery—especially in the fields of the surgery of war wounds, of chest injuries, and of the sympathetic nervous system, and in addition his wise advice was heard in the Medical Research Council and in other official bodies. His writings on surgical subjects were marked by a benign wisdom which gave them great authority, and at St. Bartholomew's Hospital he inspired during the years successive batches of students of all ages. Apart from his strictly surgical writings Professor Gask also devoted considerable attention to certain aspects of the history of medicine, and as a tribute to him over five hundred subscribers contributed towards the cost of republishing his historical essays. The work which forms the subject of this note is the public edition of this tribute.

In the historical field Professor Gask confined himself largely to the origin and development of medical schools in the ancient classical periods, to certain early aspects of the history of British surgery—and more particularly of the great English military campaigns—and to changing methods of treating gunshot-wounds of the chest. In each of these fields he enriched the subject with original material drawn from the archives, and adorned it with a style which is urbane and penetrating. This work contains reprints of ten of these essays and addresses by Professor Gask, together with the three separate Lettsomian Lectures.

The four essays on early medical schools appeared between 1939 and 1941 in a journal which is not now very easy to obtain. Although a considerable amount of work has been done on this subject since they appeared, these essays can still be considered of great importance and a very reasonable exposition of the whole question. On the knotty problem of whether Herophilus and Erasistratus did or did not vivisect human subjects, Professor Gask rightly pointed out that Erasistratus would not have said that arteries contain air and not blood if he had ever dissected living men. It is surprising how this myth—based entirely on the statements of Tertullian, a very unreliable witness, and of Celsus—after so many centuries still requires to be refuted, but this is unfortunately the case.

In those essays on the medical staff of Edward III and of the army during the victorious campaign of Henry V, Professor Gask has dug deep into original sources, and has in some respects opened up a new vista of the warfare of these days. The same may be said of his essay on Marlborough's campaigns.

A hitherto closely shrouded period in the life of John Hunter was illuminated by Professor Gask in 1937, when he dealt learnedly with the Loudon Letters, which had recently been purchased by the Royal College of Surgeons. These papers are of first importance, and they show, for example, that during the expedition to Belle Isle and the campaign in Portugal Hunter never obtained the post of deputy medical director which he so much desired. It will be news to many that during that campaign female nurses were employed, and that they were paid just half as much as the washerwomen to the troops.

Perhaps the most important essay in this book is Professor Gask's Vicary Lecture, in which he combed the original sources and State papers for information on the shadowy figures of Vicary's predecessors.

The editors of this work have accomplished their task well, and the result is a volume which will be treasured by Professor Gask's many friends and a much wider circle.

E. A. U.

Correspondence

Appendicitis in the Navy

SIR,—I was very interested to read Surgeon Vice-Admiral Sir Sheldon Dudley's letter (January 20, p. 136). I have no figures regarding acute appendicitis in ships of H.M. Fleets, but the last occasion that I operated at sea was in November, 1937, five days out from Colombo on the way to Australia aboard *S.S. Orama*. I was called to see a woman who had been ill for a week with acute abdominal symptoms. The ship's doctor, a London Hospital man, and steeped in the Sherren "wait and see" methods, had treated the woman with a minimal amount of morphine. When I saw her she was very ill with a tender distended abdomen, continuous vomiting, and a distressing diarrhoea, mucous in type. She was very dehydrated. The condition was one of very obvious general peritonitis. I operated with the assistance of a young Australian surgeon who was returning home after having gained his F.R.C.S. The peritoneal cavity was full of pus, the appendix was gangrenous and perforated. The patient made a protracted recovery, was landed at Melbourne, and, I was informed, did well. Such a case as this would have died if operation had not been performed.—I am, etc.,

London, W.1. CECIL WAKELEY.

Colonial Medical Service

SIR,—I have read your leading article (January 13, p. 78) and now, as chairman of the Colonies and Dependencies Committee of the British Medical Association and a former member of the medical service in East Africa, ask your permission to supplement it with the following practical observations. As a preliminary, however, I would remark that it is Britain's duty to provide a good medical service in her Colonies, and in these difficult times the Colonial Medical Service needs all the help we can give it. For its part the Colonial Office is undoubtedly aiming to make conditions attractive to the best type of young doctor.

There is no doubt that remuneration for the medical officer compares favourably in all the large Colonies with remuneration in the National Health Service at home. You yourself gave a striking illustration of this. Where the cost of living overseas is higher than in Britain a cost-of-living allowance is paid. Remuneration in the small Colonies is not so good, but many of these have attractions other than salary. As regards specialists, I confidently expect improvements in the near future.

Leave, study leave, and passage arrangements are generous. Your leading article pointed a warning finger at bureaucratic administration. There have undoubtedly been examples of this in the past and no doubt there will be some in the future. I am satisfied, however, that the Colonial Office is trying to correct this; and in any case, are there no examples of soulless bureaucracy in England, in the National Health Service or the public health service?

Medicine in the Colonies offers an immense and fascinating field of clinical work and research and the Colonial Medical Service has great achievements to its credit. The medical officer in charge of a district hospital can be surgeon, physician, obstetrician, pathologist, or all four at once. He will also be medical officer of health of his district. A man of all-round interests and capabilities should be happy in the Colonial Medical Service.

Life overseas, though relatively unsophisticated, offers refreshing freedom from the cramping conventions and material restrictions of Britain to-day. For those who are interested in sport and games the Colonies offer far better opportunities than Britain.

There are, of course, difficulties in colonial life, but none of them need deter any man of spirit. To any displaced registrar or unestablished practitioner I would say: "Think carefully about the Colonial Medical Service" and to any young doctor searching for a career I would boldly say: "If you have an ounce of the spirit of adventure, take your courage in your hands and go out to the Colonies."—I am, etc.,

Petersfield, Hants. JOHN L. GILKS.

Registrars

SIR,—Two particularly serious points arise over the proposed dismissal of registrars. The beginning of the Nazi movement in Germany was attributed years ago to an onslaught of unemployment among graduates in the professions. The historian may have misread the facts and history need not repeat itself. Secondly, we are about to witness the errors of the administrators—political, medical, and lay (and no purpose is served by apportioning the guilt)—being visited upon innocent individuals. This is probably a sign of the rotten core in the political philosophy of our generation. Would reprieve be too quixotic, chivalrous, old fashioned, expensive? Perhaps the country is too poor now to behave like a gentleman.—I am, etc.,

Dundee. A. C. LENDRUM.

Atypical Pneumonia

SIR,—I am indebted to Colonel L. W. Harrison for his interesting letter (January 13, p. 89) drawing attention to an omission from my article on primary atypical pneumonia (December 30, 1950, p. 1461). I was aware that the serum from cases of this condition did, at times, give a positive Wassermann reaction, and this fact should obviously have been mentioned. When in the recent war I was making a serological survey of primary atypical pneumonia, principally with the object of assessing the part played by viruses of the psittacosis group in the causation of this syndrome, Dr. Richardson, who was then Director of the Medical Research Council's Serum Reference Laboratory, examined a number of these sera for me. He was interested in the question of false positive Wassermann reactions and he found that some of the sera from atypical pneumonia gave a false positive reaction. This observation was not published and I am not in possession of the records of his findings, but my recollection is that the sera from atypical pneumonia that behaved in this way were few in number. I doubt, therefore, whether syphilitic serum tests would be of any great help either in differentiating cases of primary atypical pneumonia from other pneumonias or in the subdivision of the atypical group.—I am, etc.,

London, E.1. S. P. BEDSON.

SIR,—I should like to express my appreciation of Professor C. H. Stuart-Harris's article on atypical pneumonia (December 30, 1950, p. 1457). It is timely to be reminded of this when every day we see fresh cases of febrile lung infection, many of which are difficult to classify. For some time I have wondered whether the notification figures reflect anything like the true picture of pneumonia incidence nowadays. I think it would be helpful to general practitioners if Professor Stuart-Harris could be persuaded to write on typical primary pneumonia, briefly reviewing the diagnosis of the various types. It is my impression that in the past 12 years the clinical picture of pneumonia has changed considerably, and many practitioners who qualified in the pre-sulphonamide era must find themselves in doubt when examining early acute lung infection. Cases so often present the physical signs of pneumonia but lack the dramatic facies which characterized the disease 15 or 20 years ago.

I qualified in 1935, and at that time it was considered that the typical lobar pneumonia case could be diagnosed from the foot of the bed. Often the patient was a young adult, without previous lung pathology, who had become ill with characteristic suddenness. The decubitus, colour, rapid alar breathing, and painful cough could not be mistaken. Indeed, one was discouraged from carrying out any but a brief examination of the chest to confirm the obvious diagnosis, as such patients were easily distressed and the information obtained seldom justified the movement involved.

I think that my contemporaries will agree with me when I say that I am not describing the neglected or fulminating case, but the picture often to be seen within 24 hours of the patient being taken ill. Certainly as a medical ward clerk one saw many such cases and regarded lobar pneumonia, with its intricate web of mystic treatment and nursing, as one of the medically most satisfying conditions we future general practitioners would ever be called upon to treat. In no illness was the outcome less certain nor the treatment more complex.

As a house-surgeon in 1936 and 1937 I saw less of primary pneumonia but plenty of secondary cases occurring as complications to upper abdominal surgery, often bringing into disrepute sound surgical procedures which to-day are without risk. Since 1937 and the introduction of sulphapyridine it seemed that a rapid decline occurred in the drama of pneumonia. Since entering general practice in 1939 I do not recall seeing one single case of what I was taught as a student to regard as typical lobar pneumonia. That I have treated scores of pneumonias I am in no doubt. In a practice of maximum numbers scarcely a week goes by in the winter without my seeing one or more of these incipient cases of early primary pneumonia. A patient feels ill. He has fever and a slight cough. He may have discomfort in the chest. Probably he has had a slight rigor. On examination he looks cheerful and comfortable in bed. He may be reading the paper. His colour is good, temperature 101° F. (38.3° C.), pulse rate 90, and respiratory rate 18. There are signs of upper respiratory tract infection. The respiratory movements of his chest are normal, but at one lung base there is diminished air entry and a band of undoubted crepitations. In such a case one is tempted to borrow the old term "congestion of the lung," although if the lung could be examined the developed pneumonic process would be seen. If adequate and intelligent administration of sulphonamide is started forthwith one can expect, as much as one can count on anything in medicine, that in 36 hours the temperature will return to normal and any toxic signs will disappear. The physical signs in the lungs may extend a little in the first 24 hours, but thereafter their progress is arrested and in five to seven days they have disappeared entirely. Is this the acute lobar pneumonia notifiable to the medical officer of health?

I have omitted any reference to the many cases which occur in established bronchitics and those whose chests will at all times provide a cacophony of signs and sounds denoting chronic upper and lower respiratory tract catarrh superimposed on a background of emphysema, asthma, or bronchiectasis. In such cases it is more difficult to assess the degree of lung infection and to determine the point at which bronchitis becomes notifiable pneumonia.

Only in the case of infants and young children can it be said that the early case of pneumonia retains its pre-sulphonamide appearance. In them one can still see the distressed appearance, restlessness, bad colour, and rapid alar breathing characteristic of rapid invasion by a virulent infection.

My feeling is that the incidence of attenuated primary pneumonia has increased very considerably in the past ten years but that this increase is not reflected in the notification returns. Practitioners are reluctant to label early acute lung infection (as above described) as pneumonia because the initial symptoms are so mild and because the disease can be arrested overnight by the institution of antibiotic treatment, and the whole clinical picture dissolved in 48 hours. It is in these rather indeterminate cases that we should appreciate Professor Stuart-Harris's opinions and recommendations on diagnosis and nomenclature.—I am, etc.,

Sheffield. E. C. ATKINSON.

Idiosyncrasy to Tubocurarine

SIR,—The following case of idiosyncrasy to 6 mg. D-tubocurarine chloride may be of interest, occurring as it did in a seemingly amyasthenic and disease-free individual of normal build.

T. Cecil Gray (1947) and Gray and Halton (1948) reported two cases of idiosyncrasy, or exaggerated response, to the administration of 15 mg. of D-tubocurarine chloride (with thiopentone 0.5 g.). Both patients had advanced carcinoma of a bronchus, and each had atelectasis of a lung. Gray and Halton thereafter employed a test-dose method, injecting 5 mg. curare routinely before induction to detect any exaggerated response; later they encountered another patient, preparatory to thoracoplasty, who was rendered apnoeic and curarized by 6 mg. curare.

A woman, aged 48, in whom no clinical abnormality was detected pre-operatively, with Hb 88% (Haldane), was to undergo total hysterectomy and bilateral salpingo-oophorectomy for functional uterine haemorrhage. Premedication: "omnopon" ¼ gr. (22 mg.) and scopolamine 1/300 gr. (0.22 mg.), one hour before operation. Induction: thiopentone 0.3 g., followed by N_2O and oxygen.

The patient was then placed in the lithotomy position for vaginal swabbing and catheterization. Just before completion of the latter a test dose of 6 mg. curare was given, and apnoea resulted which lasted for 15 minutes after the skin incision was made.

The operation was completed 75 minutes after the administration of curare. As intercostal paralysis still persisted, prostigmin 2.5 mg. and atropine sulphate 1/100 gr. (0.66 mg.) were injected intravenously, resulting in satisfactory respiratory exchange within two minutes. Post-operatively her general condition was good, and she had a smooth, uneventful convalescence.

—I am, etc.,

Hayes, Middlesex. H. HOWELL-JONES.

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Sulphonamide Sensitivity

SIR,—I wonder if your readers would be interested in a somewhat unusual case of sulphonamide sensitivity?

The patient, a man aged 25 years, an electrician by trade, complained of a pain in his right ear. The condition was diagnosed as an otitis externa, and a swab was taken which showed a mixed infection of *Pyocyaneus* and haemolytic streptococci. He was treated with streptomycin drops and put on a course of "sulphatriad." After taking 12 tablets (6 g.) he noticed an itching in his finger-tips, which was followed by the eruption of bullae over the sites of old injury.

The bullae were situated as follows: Left forearm size 2 in. by 1½ in. (5 by 3.7 cm.), over the site of a burn dating from June, 1940. He was rather vague about the treatment of the burn, but said his doctor had used a yellow ointment. Right knee, size 2 in. by 1½ in., the site of an old abrasion which had been treated with penicillin cream, had healed, been reopened, and later treated with sulphonamide cream. Lower part of right leg, 1½ in. by 1½ in. (3.2 cm.), the site of a burn in August, 1950, which was treated with sulphonamide powder and tulle gras.

The itching of his finger-tips also occurred over the sites of old injury (burns), but there were no vesicles or bulla formation. Treatment consisted in aspiration of the bullae, tulle gras dressings, and "benadryl" 50 mg. twice daily.

—I am, etc.,

Bahrein. J. KINSELLA.

Erythrocyte Sedimentation in Anaemia

SIR,—Dr. H. S. Kellett has described (December 23, 1950, p. 1445) the familiar "correction" dogmas at such length that I must ask your permission to reply in detail. As I see it, Dr. Kellett and many other clinical pathologists will continue to believe in "correction" as long as they continue to study the problem in the seclusion of their laboratories, and thus they will continue to mystify and mislead their clinical colleagues with reports of normal (corrected) E.S.R.s in cases of grave disease. In the laboratory it is difficult to avoid noting the frequent coincidence of anaemia and increased E.S.R. and hence deducing that the increased sedimentation is related to the anaemia: it is then natural to formulate an appropriate theory. The clinician, having his patient constantly before him, is more impressed by the relation of both the anaemia and the abnormal E.S.R. to disease rather than to one another.

Dr. Kellett's whole argument rests upon his statement, "*If it is assumed that the plasma 'sedimentin' concentration is the same in anaemic blood as in normal blood . . .*" It is difficult to discover a more unjustified assumption in the literature of sedimentation correction, which is full of assumption. The concentration and nature of sedimentin clearly varies according to the cause of the anaemia: in anaemia due to infection and new growth there is increased fibrinogen and the increased E.S.R. is abolished by defibrination; in the anaemia of myelomatosis and kala-azar increased sedimentation is chiefly due to increased globulin and defibrination has little effect; while in the anaemia of simple blood loss the evidence that I have submitted (December 9, p. 1296) indicates a possible decrease in sedimentin. Since all Dr. Kellett's conclusions stem from this assumption of sedimentin concentration remaining unchanged in anaemia, I submit that they are all equally fallacious.

Other statements in his letter call for comment:

"*Unlikely that the size of the cell will be an important factor.*" With this Dr. Kellett dismisses the possibility of the red cells having any effect, but there is plenty of evidence to the contrary, to which I referred in my article (Bunting, 1939; Ham and Curtis, 1938; McFarlane and O'Brien, 1946).

"*The E.S.R. depends upon the amount of sedimentin acting on the total surface of the erythrocytes.*" This is pure speculation, and is in my opinion incorrect, but if true it would contradict Dr. Kellett's own theories, since in equal P.C.V.s in pernicious anaemia, normocytic anaemia, and hypochromic anaemia there are different totals of cells and of cell surfaces—yet Dr. Kellett's correction would be the same in each instance.

"*A series of bloods from cases of uncomplicated idiopathic hypochromic anaemia.*" First, the clinician often has difficulty enough in deciding whether or not a case of hypochromic anaemia is complicated and the pathologist must find it well-nigh impossible. Secondly, hypochromic anaemia is virtually never idiopathic.

"*In 50% . . . I found the E.S.R. increased in proportion to the degree of anaemia.*" I suggest that the real cause of the increased E.S.R.s in these so-called uncomplicated cases may well have been overlooked if the clinicians dependent on Dr. Kellett's reports accepted his normal (corrected) results at their face value.

"*In the other 50%, the E.S.R. was raised considerably less than might have been expected from the P.C.V.*" I am most interested to learn that 50% of Dr. Kellett's cases failed to support his own theory, even using Wintrobe's technique, and I submit that this is relevant additional support for my own conclusions. Moreover, I cannot help wondering what percentage of incompatible facts Dr. Kellett requires before he begins to doubt his theory.

"*The finding of normal results fairly constantly in anaemia.*" To be applicable to my findings, this should have read, "in uncomplicated hypochromic anaemia."

"*Other authors who oppose correction have . . . used . . . citrate as an anticoagulant.*" The authors quoted in fact did not all use citrate, neither did they all oppose correction. Schuster (1938) did not oppose correction; she opposed charted systems of correction, advocating instead manipulation of the red-cell count to normal before estimating the E.S.R., an obviously fallacious procedure. Day (1939) only opposed correction in mild degrees of anaemia, basing his opinion on some rather obscure experiments. Smith (1938), using a capillary tube technique, opposed correction in the nutritional anaemia of children. Davis (1946) accepted correction with some techniques and stated: ". . . Long recognized that oligocythaemia accelerates sedimentation and polycythaemia retards"; however, it would be fair to say that he is obviously sceptical of correction. Gram (1929) and Walton (1933) used citrate and submitted their own methods of correction. Those who did oppose correction unfortunately did so in uncertain fashion and with little or no supporting evidence.

"*Sinclair and Duthie (1950) obtained results suggesting that anaemia was having an effect on the E.S.R.*" The suggestion is entirely Dr. Kellett's, for the authors carefully pointed out that there was "no readily acceptable explanation" of the effect of intravenous iron on the E.S.R. of rheumatoid arthritis.

My conclusion regarding the lessened stabilizing effect of citrate in anaemia is dubbed as fallacious, on the pure assumption that the effect of citrate depends on the amount of citrate per erythrocyte. There is no reason to regard this assumption as valid and it is certainly not borne out by the results of dilution experiments (December 9, 1950, Table V, p. 1299).

Correction is "*necessary in theory, but not necessary in routine clinical work.*" Thus Dr. Kellett neatly summarizes this conflict of mind produced by the attempt to relate obstinate facts to untenable theory. I wonder how long he will continue trying to have it both ways.

May I take this opportunity to point out my error in stating that the correction chart of Whitby and Britton (1946) was based on dilutions of normal bloods, whereas in fact it was based upon manipulations of anaemic bloods. My error, however, in no way affects my arguments, for an anaemic specimen concentrated to normal P.C.V. no more resembles normal blood than a normal specimen diluted to a low P.C.V. resembles anaemic blood.

In my opinion, if the pathologist reports the actual (observed and uncorrected) E.S.R. as well as, if he wishes, the "corrected" (i.e., masked) E.S.R., no great harm is likely to occur, for most clinicians have for long felt sceptical of the correction theory; but the pathologist shoulders an enormous responsibility if he reports only a normal (after correction) E.S.R., when the (uncorrected) abnormal E.S.R. may be the only indication of serious disease.—I am, etc.,

London, E.C.1. RICHARD TERRY.

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Loss of Vision

SIR,—In your leading article "Loss of Vision" (December 30, 1950, p. 1482) you say (p. 1483) of partially sighted persons, "Such registers are now coming into use and are undoubtedly serving a useful purpose." Maybe that is correct for an ideal district, which has sufficient welfare services at its disposal, sufficient ophthalmologists to certify, and efficient home visitors and other welfare staff who are competent to select persons to be referred for certificates. It certainly does not apply to my area. What useful purpose can be served, when a person is certified as partially sighted, if the training facilities of the local authority are totally inadequate even for the totally blind people? If no special ophthalmologist is employed for certifications, then the whole burden may be placed on the School Eye Service. Not the slightest discretion is used by some welfare officers when recommending certification: any person applying for public assistance is referred to me for certification if there is the remotest chance of some eye trouble. People whose vision would be fair or even normal with glasses, but who have never bothered to see an optician, are also referred to me for blind certification. On the other hand a glaucoma patient who has not himself the sense to seek medical advice (many old people have not) will never be advised by the welfare officer to do so. He may have to wait some months till he sees me. People who have lost one eye but whose other one is normal or nearly normal in vision, and those with an acute inflammatory condition, are all referred to me for certification: nobody dreams of arranging treatment or advising the patient to seek his doctor's advice.

The result is that the children's eyes are terribly neglected, because I cannot cope with all these cases. Innumerable eyes that squint undoubtedly go blind if not attended to in time, and myopic ones suffer harm (although they do not become blind) if they are not seen annually but have two, three, or more years to wait. But if a Certified Blind person wants his worn-out glasses replaced, which could easily be done by any optician under the supplementary ophthalmic service, at least in areas where opticians or even hospitals are close by, I have to refract him with highest priority. I get advanced cataracts referred for refraction, among them people who have been told previously in a hospital that they cannot be fitted with glasses. Such cases are a perfect waste

of time. I have no idea of the patient's condition beforehand, and the clinic's time has to be allocated no matter whether I can do something for the patient in the end or not. I get people to certify who have glasses on order with which their vision is fair, and people who are about to enter hospital for operation in the very near future. Could they not wait till treatment is finished, so that I have not to decertify them afterwards again, while children's eyes go blind through neglect?

Finally a point of a different kind. Why was "place of examination" omitted in the new B.D.8s? Is it not most important for the validity of the certificate whether the examination was made in a decent clinic or an improvised clinic without proper light and space, or in the patient's home, as was the rule in the good old days?—I am, etc.,

SCHOOL OCULIST.

Popliteal Ligation for Post-phlebitic Leg

SIR,—In my paper (December 9, 1950, p. 1307) I endeavoured to investigate popliteal vein ligation in as dispassionate a way as possible. Mr. S. M. Rivlin in his letter (December 30, p. 1495) lists me as its protagonist; he is certainly an antagonist, presumably because his results have been unfortunate.

I like to think that if he selects his cases along the lines I suggested, even if he does not stoop to measure the erect venous pressure during exercise, he will get better results. In a condition like post-phlebitic leg it would be asking too much to expect any one measure to cure, as we cannot remake valves. If however a measure in properly selected cases can cause relief in a considerable proportion, he would be a poor physician who would withhold such a remedy because eventually its good effects might cease. I agree of course with Mr. Rivlin that there is no guarantee that these cases will not subsequently relapse, but surely even a passing relief is worth while.

Mr. Rivlin has missed my point in the aetiology of the condition. Essentially the normal venous pumping mechanism has failed, but there is no evidence that the flow in the incompetent vein is retrograde in exercise. The normal person when standing is always moving slightly from foot to foot, and this exercise is sufficient to keep the venous pressure low. Depending upon the extent of valvular failure, the pressure rises, and it is this raised pressure in the erect position which causes the trouble. It is well known that if all these patients are kept in bed irrespective of what is done to the veins good results will ensue, and it is readily demonstrable that when lying in bed the pressure is very low. By tying the popliteal vein the strain is, of course, put on the collateral veins, but it must not be tacitly assumed that they must become incompetent.

As to Mr. Rivlin's query regarding the eleven satisfied clients, they included the earliest and latest of the series and the remainder are scattered in between.—I am, etc.,

Leeds. A. J. WALKER.

Treatment of Tinea with Oral Sulphone

SIR,—An Indian labourer, about 40 years of age, had suffered from tinea corporis for 15 years, resisting a great variety of treatments. These included iodine, mercury, chrysarobin, salicylic acid, benzoic acid, and gentian violet. The whole of the trunk, upper parts of the arms, buttocks, and legs showed contiguous circular patches which healed at the centre and spread at the periphery. There was no anaesthesia, nerve thickening, or lepromatous tissue to suggest Hansen's disease (leprosy). Because of the marked resistance to other treatment and the fairly high concentration of sulphones obtained in the skin, diaminodiphenylsulphone (D.A.D.P.S.) was given in dose of 0.1 g. daily for the first week and 0.2 g. daily thereafter. By the end of the second week no trace of tinea existed. The success of sulphone in this case may be of interest to others, as this type of resistant fungus infection is not uncommon in the Tropics.—I am, etc.,

Doom Dooma, Upper Assam. P. H. BIRKS

Oedema of the Glottis

SIR,—The rare clinical phenomenon known as acute oedema of the glottis (see December 30, 1950, p. 1476) or, more correctly stated, of the introitus laryngis (arytenoids, ary-epiglottic folds, and ventricular bands) may result not only from a sting or other physical trauma but from any localized or proximal infective condition, and, as pointed out by Dundas Grant, the presence of acute dysphagia and laryngeal stridor in the absence of obvious inflammation in the oro-pharynx must incriminate the hypo-pharynx and (or) the introitus laryngis, the early recognition of which is of such supreme prognostic importance.

As regards expectant treatment, if such be ever justifiable, the frequent local application of a weak solution of cocaine and liquor adrenalin, in equal parts by spray or otherwise combined with the intravenous injection of calcium gluconate supplemented by parenteral antibiotic treatment would be most likely to effect the requisite rapid improvement. In view, however, of the vital urgency of these cases, the rapid relief which it effects, and the ease with which it can be performed, scarification or multiple puncture of the oedematous supra-laryngeal structures is the treatment of choice. It can be carried out after the topical application of cocaine adrenaline solution by means of a laryngeal knife or, alternatively, a long-handled curved bistoury and a tongue-depressor. A frontal mirror is desirable but not a *sine qua non*. From personal experience I can vouch for the relative effectiveness of this procedure in comparison with the technically much more difficult and risky tracheotomy.—I am, etc.,

Cork. J. B. HORGAN.

Certification

SIR,—Now that we have an epidemic upon us it seems to me that the absurdity of the method of certification is demonstrated. It cheats both patient and doctor alike, the first of his money and the second of his time and proper function. "I wouldn't have troubled you, Doctor, to call, but I must have certificates before such and such a day." The malady of certification has now spread to industry: "I'll lose my job or holiday money, etc." My visiting list, already too long, could have been halved this week but for the need of certificates—a sheer waste of time and talent.

Might I suggest that the sick-visitor could be employed to visit the sick and witness the facts that the patient is in bed and to the lay observation sick, and report them to the necessary authority? The doctor could then if needed call when more pressing professional needs have been attended to.—I am, etc.,

Wrexham. E. A. R. EVANS.

Shorter House Jobs

SIR,—As a student may I submit that a possible remedy for some of the deficiencies in our training as future G.P.s would be the shortening of house appointments in some specialist hospitals? If, for instance, it were possible to work for only two to three months in, say, a fever hospital, it would give a greater number of budding housemen a fair chance to see some of the cases they have up till now only read of, and prevent some of the crass errors of diagnosis so frequently made by beginners.—I am, etc.,

London, S.W.10. H. KELSON FORD.

Oral Penicillin

SIR,—Dr. S. A. Doxiadis and his colleagues (January 6, p. 16) state, from observations carried out on *healthy* subjects, that if penicillin is given by mouth very large doses must be administered in order to obtain an adequate level in the blood, because the hydrochloric acid of the stomach destroys penicillin. But in virtually all the conditions for which penicillin is used there is no hydrochloric acid in the stomach, its secretion being temporarily inhibited by the toxic condition of the body (Faber, K., *Gastritis and Its Consequences*. Oxford, 1935). The oral administration of penicillin, both for children and adults, has many advantages

not only to the doctor but also to the patient. Therefore before assuming this form of therapy is unsatisfactory, or too costly, or to require in addition large amounts of antacids, it would seem important that blood penicillin levels after oral doses should be investigated during illness and not during the irrelevant condition of health.—I am, etc.,

London, W.1. FRANKLIN BICKNELL.

Poliomyelitis in London in 1949

SIR,—We are glad to assure Dr. E. H. R. Smithard (January 13, p. 92) that for all statistical purposes in our paper (December 30, 1950, p. 1473) the number of confirmed notifications of poliomyelitis in Lewisham in 1949 was taken as 35, the figure he quotes as correct. A table showing the basic distribution by boroughs was prepared for publication, but could not be included for lack of space. We used for all calculations the figures given, as confirmed, to the Registrar-General by the borough medical officers of health in their quarterly returns; we hope there is no danger in this indirect aggregation, otherwise the Registrar-General's publications are presumably also implicated. The map was plotted day by day (for purposes other than the paper), and where the daily returns from the borough medical officers of health showed earlier notifications to be unconfirmed the cases were erased. In this sense the map was bona fide corrected. Only eight such corrections were received from Lewisham. We doubt whether the pictorial impression is substantially in error, but we apologize for the fact that no note was added to the diagram pointing out limitations in the meaning of "corrected."

With regard to the confirmed cases for 1950, quoted by Dr. Smithard as 32, we would add that for the first three quarters alone, according to copies of forms received by the L.C.C., he had returned 32 cases to the Registrar-General—i.e., equal to his present total for the whole year.—We are, etc.,

G. E. BREEN.
London, S.E.1. B. BENJAMIN.

Management of Thyrotoxicosis

SIR,—Dr. Raymond Greene (December 16, 1950, p. 1378) attributes to me an opinion far stronger than anything I should care to hold. He writes that I asserted at a meeting of the Section of Endocrinology of the Royal Society of Medicine that all patients who had had remissions of thyrotoxicosis following medical treatment would eventually relapse.

What I said in this respect was apropos the remark of a previous speaker who mentioned the "cures" obtained by physicians in the days before thiouracil came into vogue. I stated that, in my experience, there was a proportion of patients in whom the disease was episodic, and that I had operated upon a number who had undoubtedly had the disease in a severe degree many years previously, and who had been apparently temporarily cured by rest and sedatives. I added that, to my knowledge, no physician had published a long-term follow-up of such "cures." I should be surprised, however, if some patients did not remain permanently well in a disease so varied in its course and so differing in intensity.—I am, etc.,

London, W.1. CHARLES DONALD.

Acetonuria Rare

SIR,—In their article (January 6, p. 14) "Raised Blood Pyruvic Acid Level in Diabetic Acidosis" Drs. I. C. Gilliland and M. M. Martin make the curious statement that the urine was loaded with sugar and acetone (FeCl, test). I think the authors mean that a large amount of aceto-acetic acid was present in the urine and that the FeCl, test gave a deep port-wine colour. But their statement is meaningless for the following reasons:

(1) Acetone is not present in freshly passed urine, but only appears if the urine is allowed to stand for some time, when some of the aceto-acetic acid decomposes to acetone.

(2) It is impossible to produce air hunger with acetone in a cat, whereas aceto-acetic acid is the substance which causes air hunger.

(3) Acetone does not give any colour with FeCl, solution, whereas aceto-acetic acid gives the port-wine colour.

Rothera's modification of Legal's test (*J. Physiol.*, 1908, **37**, 491) is a test for acetone and aceto-acetic acid, although Rothera thought it was a test for acetone only. It is, however, a much better test for aceto-acetic acid, and Hurtley (*Lancet*, 1913, **1**, 1160) showed that acetone could be detected in a concentration of 1:20,000, whereas aceto-acetic acid could be detected in a concentration of 1:400,000.

Many people, who do not know that acetone, though expired by the lungs, is not excreted in the urine, speak of acetonuria instead of ketonuria. But it is a pity that the authors should make such an inaccurate statement in an otherwise interesting and excellent article.—I am, etc.,

London, W.1. GEORGE GRAHAM.

Refresher Course

SIR,—Reading with the greatest interest your two refresher course lectures on disk lesions (December 23, 1950, p. 1434) and acute bronchitis (January 13, p. 82), I find one must review the meaning of the word "refresher." Here we see our well-tried remedies for backache tossed in the bucket, and tracheotomy threatened for croup in lieu of ipecacuanha wine. There is no refreshment of our knowledge of medicine in all this. Must we divorce urban therapeutics from rural therapeutics? The healing urge of nature, so delightfully obvious in country practice, appears to be entirely absent in the out-patient departments and wards of the great hospitals. In such hospital experience, where the specialist meets his human material at the syringe point, little co-operation with nature can be expected. It is presumed the natural healing powers will not respond to trauma, bacterial or otherwise. Chemotherapy usurps the field.

We country workers, who still appreciate the help of providence, cannot expect specialists to understand how we treat and cure the myriads of patients they are never privileged to see. If they understood, we might escape some of their sweeping condemnations.—I am, etc.,

Hexham, Northumberland. RICHARD BELL.

What is Homoeopathy?

SIR,—What is homoeopathy? Is it scientific or mumbo-jumbo? We read little about this subject in the *Journal*, and I for one am confused about its relation to orthodox medicine. If it has something real to offer, let us hear about it, but if not should it be relegated to the status of naturopathy?—I am, etc.,

London, W.13. R. E. W. OLIVER.

POINTS FROM LETTERS

Long Umbilical Cord

Mr. A. E. CHISHOLM (Dundee) writes: Several years ago I had a case in which the umbilical cord measured 5 ft. with two true knots, both quite loose. The cord had not twisted round the baby and there was no complication.

Red-cell Stippling in Poisoning

Dr. A. PINEY (London, W.1) writes: Dr. W. Gross (December 30, 1950, p. 1496) says that in patients treated with bismuth or mercury "supravital staining with brilliant cresyl blue revealed basophil stippling of the red blood cells." It is essential to realize that punctate basophilia (stippling) of red corpuscles can be seen without any staining, whereas the basophilic substance seen after vital staining is something quite different, being indicative of immaturity of the corpuscle, not of degeneration. Dr. Gross need thus not be surprised that he was unable to find any reference to basophil stippling of red blood corpuscles in bismuth and mercury poisoning. There are, however, many references to the presence of reticulocytes—i.e., corpuscles which with vital staining can be seen to contain a basophilic substance, sometimes in the form of dots, but more usually in a skein.

Obituary

G. E. GASK, C.M.G., D.S.O., F.R.C.S.

Professor G. E. Gask, consulting surgeon to St. Bartholomew's Hospital, died at his home at Hambledon, Henley-on-Thames, on January 16, aged 75.

George Ernest Gask was born in 1875 and was educated at Dulwich College. He entered the medical school at St. Bartholomew's in 1893, qualifying M.R.C.S., L.R.C.P. in 1898. After working as house-surgeon to Mr. John Langton, he was appointed demonstrator of pathology, then surgical registrar, and later, in 1907, assistant surgeon.

He had become a Fellow of the Royal College of Surgeons in 1901. For five years, from 1906 to 1911, he was warden of the residential college at Bart's. When the first world war broke out he was a successful consultant surgeon. Serving first as a Territorial officer at the 1st London General Hospital, he went to France in 1916 as surgeon to a casualty clearing station, and two years later he was appointed consulting surgeon to the 4th Army with the rank of temporary colonel A.M.S. Mentioned in dispatches four times, he was awarded the D.S.O. in 1917 and the C.M.G. in 1919. During his war service he was particularly interested in the treatment of injuries of the chest, and after the war was over the West London Medico-Chirurgical Society awarded him the society's gold medal for his work in this field.

One of Gask's enthusiasms was to see professorial units established in the teaching hospitals. When he returned to civilian life the University of London appointed him the first director of the surgical unit at Bart's. He was later joined by Mr. Thomas Dunhill (as he then was) as assistant director, and he had as his first chief assistants Mr. Ogier Ward and Mr. Geoffrey Keynes. This unit, which was started with so strong a team, was an unqualified success, and Gask was at the head of it until his retirement in 1935. It served as a pattern for similar units formed in other hospitals.

Gask was a beautiful operator, and it was a pleasure to watch him. The outstanding characteristic of his work was gentleness, with its usual excellent results. He wrote a textbook of surgery with Harold Wilson, a book on the surgery of the sympathetic nervous system with J. Patterson Ross, who afterwards succeeded him as professor and director of the surgical unit, and many lectures, addresses, and articles in the medical press. He was always greatly interested in the affairs of the Royal College of Surgeons, serving on its council for 16 years. He was Hunterian Professor in 1930 and Thomas Vicary Lecturer in the same year. He gave the Bradshaw Lecture in 1932 and was elected a vice-president of the College in 1933. In 1937 he was special Hunterian Lecturer. The *British Journal of Surgery* owed much to him. He was chairman of the editorial committee from 1936 to 1946, and it was largely due to his influence that the committee became fully comprehensive and representative of the profession. The issue which was published last July was specially dedicated to him on the attainment of his seventy-fifth birthday. Another birthday gift was the gathering together in one volume of a number of his essays, entitled *Essays in the History of Medicine* (see p. 187). The universities of London, Oxford, Cambridge, and Bristol appointed him as an examiner in surgery, and surgical societies on the Continent and in America elected him to honorary membership. The French Government awarded him the Croix d'Officier de la Légion d'Honneur in 1937. He was a member of the Medical Research Council from 1937 to 1941, of the Radium Commission, and of the governing body of the British Postgraduate Medical School. The Medical Society of London elected him its president for a term, and in 1936 he was president of the Section of Surgery at the Annual Meeting of the B.M.A.

When the second world war broke out in 1939 he came out of retirement and assumed the duties of temporary surgeon to the Radcliffe Infirmary, Oxford, and he also became a lecturer in the university, which conferred on him the degree of M.A. by decree. The Ministry of Health called on him to act as an adviser in surgery to the Emergency Medical Service, and he made many visits to hospitals in the South of England during the course of the war. Even after his wartime duties were over he retained an interest in medical affairs, for he was chairman of the medical advisory committee of the Oxford Regional Hospital Board and of the Local Executive Council from 1947 to 1948.

He was essentially a calm, quiet, but determined man. Whether teaching, operating, or organizing, he always knew what he wanted to say and what he wanted to do. He never really appeared to be exerting himself, but he was quite untiring. He was a good judge of men and chose his assistants very carefully. His chief interests in life were surgery, St. Bartholomew's Hospital, and climbing. He was a distinguished member of the Alpine Club, being honorary secretary from 1917 to 1919. As a mountaineer, and indeed in all walks of life, he was resolute and imperturbable.

He married in 1913 Ada Alexandra, daughter of Alexander Crombie, of the I.M.S. His son is also a doctor and a Bart's man.—R. M. V.

R. O. W. writes: I first met Gask in Zermatt in August, 1906. It was at the end of my first season in the Alps. We had just climbed the Rothorn and were feeling confident, so that when our guide pointed out a group of, as he told us, very good English climbers, who were finishing their tea outside a hotel, we decided to present ourselves. One was Gask, who said little; another was Dr. Tom Longstaff, already famous for his climbs both in the Alps and in the Himalayas. The meeting was a short one, but we listened with respectful interest to replies to our various questions.

The next occasion was about two years later, when I entered Bart's as a new student and found myself in the presence of a big man who was the warden. I explained my purpose and my aspirations, and, after speaking for some time, ceased. Then followed a silence, one of the silences with which I was to become very familiar in later years—a silence in some respects resembling those ascribed by Maurois to Colonel Bramble; a silence which one could not break because

there was nothing more left which one had not already said. However, such silences differed from those of the colonel, because when Gask ultimately broke them his remark was usually one which cut right down to the root of the matter or beyond. Like Marshal Joffre, Gask was always ready to listen and, like the marshal, he would often make no comment. On this occasion he presently said, "I've seen you before." At once a contact was established. During the following years I dressed for him and his chief, Mr. D'Arcy Power. There could hardly have been a greater contrast. D'Arcy Power was extremely quick in speech and in action, above all in operating. Gask was slow to decide and in operating proceeded with deliberation from step to step—after all, you cannot hurry up a mountain. Really I think it was his unruffled calm which helped make him such a fine mountaineer and a surgeon to whom one would have at any time entrusted one's life. He was never rough, he wasted no time, but he was very careful of detail, without, however, being in any way fussy. "Fingers out of the wound: use forceps," he would say to his assistants. This was in those far-off days, long before the "no-touch technique" was thought of. I was his house-surgeon in 1913, but then saw no more of him till after the end of the war, when I had the good fortune to be appointed one of the surgical professorial unit. He had changed little and soon showed that he had faith in the new design.

In those days his name as a thoracic surgeon had been well established by his work in the B.E.F. Many late battle casualties with chronic empyemata were referred to him for treatment, and operations were undertaken with the object of removing scar tissue and allowing the lung to expand once more. These operations were long and hazardous, for in those days the modern methods of combating sepsis were not available and anaesthesia had not yet reached its present perfection, but they showed the way to what might in the future be done within the thorax, a region which hitherto the surgeon had not ventured to explore except with a needle or a tube. Bart's is by some supposed to be ultra-conservative. It would be easy to prove that this is not true; none the less it required courage to break tradition and bring Dunhill from Melbourne to join the hospital staff and to be his assistant director; but Gask was rightly sure that this step would prove a firm one, and the results which have followed in the development of the unit have amply proved that the foundations on which he established it were sound.

For some years he continued to visit the Alps; he had many great climbs to his credit and did a good deal of guideless climbing. He was invited to organize a Himalayan expedition, but found himself unable to accept. His last Alpine ascent was the Matterhorn by the Zmutt *arête*. I well remember hearing from him a modest account of how much he had enjoyed that magnificent climb and rejoiced in the sense of achievement as he stood on the summit and surveyed the landscape, feeling, as he said, for a moment like an Olympian god. Those who were privileged to work for Gask had a great affection for him.

Sir LENTHAL CHEATLE, K.C.B., C.V.O., F.R.C.S.

Dr. S. McClements writes: As an old dresser of Sir Lenthal Cheatle, I would like to place on record some of the qualities that endeared him to his students and patients. The former he treated as co-equals with himself when investigating cases and always paid the greatest attention to a student's observations—not infrequently admitting, during a laparotomy, that one of his dresser's observations had been quite correct, while his own had been erroneous. Always stressing the importance of accurate and detailed observations by his dressers, he did not put full reliance on the textbook picture of disease. He was a stimulating teacher with an unorthodox outlook on certain aspects of operative surgery. His personal reminiscences of Lister were always a source of great interest and inspiration to students. To patients he was always courteous and polite, and often a ten-shilling note found its way to a poor man's pocket. Always immaculately dressed with top hat and morning coat, he appeared one of the last survivors of the age of elegance.

J. H. RAWLINSON, F.R.C.S.Ed.

News of the death of Mr. J. H. Rawlinson on January 14 has caused sorrow and grief among a wide circle of friends and colleagues throughout Merseyside. James Herbert Rawlinson was a student at Liverpool University, and he graduated M.B., Ch.B. with honours in 1907, being awarded the Canthac Medal. He then held several resident posts, and was chosen a Robert Gee Fellow of Anatomy at the University of Liverpool in 1912. A year later he was appointed resident surgical officer to Bradford Royal Infirmary. Just as war broke out in 1914 he was elected assistant general surgeon to the Northern Hospital, Liverpool, but, as was so characteristic, he volunteered for the R.A.M.C. immediately and served as a surgical specialist in France until 1918. On return to civil life he took up his post at the Northern Hospital, and for the next 27 years this was the centre of his interests and devotion and around which he built an extensive practice. He became a Fellow of the Royal College of Surgeons of Edinburgh in 1923. His abilities were widely recognized, and for many years he served on the staffs of the Ormskirk General Hospital, Bootle General Hospital, the Hoylake Cottage Hospital, and Port Sunlight Hospital. In 1932 he was appointed to the senior staff of the Northern Hospital and became a member of the university faculty of medicine. In 1946, in accordance with custom, on attaining the age of 60, he retired from the active staff of the Northern Hospital but continued to work at the Hoylake Cottage Hospital and later at St. Catherine's Hospital, Birkenhead, and Wallasey Central Hospital. He was an interesting and inspiring teacher with a clear and orderly mind, and his object was to make good doctors rather than good examinees, though in fact he achieved both. He much preferred informal bedside teaching to the prepared lecture, and his crowded senior ward rounds will long be remembered with gratitude by successive generations of students and house-surgeons.

In consultation his manner was impressive but kindly and inspired confidence. His approach to surgical problems was always logical and his judgment reliable. He was essentially a general surgeon with a special interest in abdominal and urinary surgery, and as an operator he was deliberate, skilful, and speedy. His loss will be felt particularly by his junior colleagues, who held for him the greatest respect and the deepest affection. They could always turn to him with complete confidence in any case of difficulty, knowing that their patient's interests and their own were in safe keeping. He will be sadly missed by a large group of doctors who recognized in him not only an outstanding surgeon but a

staunch friend on whom they could rely and who at all times was prepared to help them, day or night. He was essentially a man of activity, and he was busily occupied in his practice when at Christmas his last short illness began. Probably that is what he would have chosen himself, for he was soon to retire, and, although keenly interested in music, literature, and golf, surgery was his life's interest, and without it he would not have been happy.—P. H.

Dr. R. J. Minnitt writes: I have enjoyed the friendship of J. H. Rawlinson for almost 40 years, and I can testify to his sterling qualities as a man. Forthright in his attitude towards current problems which affect professional and hospital administration, some may have thought him unconventional, but he was absolutely honest and sincere in all that he said and did. He was one of those belonging to a tradition and age which most regretfully is fast passing away, but he has left a shining example and memory to succeeding generations which will be an inspiration for many years to come.

Dr. WILLIAM JAMIESON LOGIE died on December 6, 1950, at his home in Falkirk. His father was the late Bailie W. J. Logie, and he studied medicine at Glasgow University, where he graduated M.B., Ch.B. in 1905. He was keenly interested in pathology, and was appointed to the pathological staff of Glasgow University under Professor Robert Muir. Later he obtained a lectureship in pathology and bacteriology at the University of Birmingham, where he was also visiting pathologist to the General Hospital. Eventually he settled in Falkirk, where he succeeded the late Dr. McCracken in general practice and was appointed bacteriologist to the Falkirk and District Royal Infirmary when the new building was completed. A member of the Pathological and Bacteriological Society of Great Britain and Ireland, he did much original and valuable research on dysentery before the first world war. He had many and varied interests outside his profession, being a Chopin enthusiast and a pianist of no small merit. He was a serious student of astronomy and modern scientific research. At the time of his death he was the president of Falkirk Burns Club. When the first nursery school was started in Falkirk Dr. Logie was appointed its chairman—a post which he held till his death. His kindly presence will be greatly missed by his colleagues.—A. E. H.

Dr. CHARLES ROBERT WORTHINGTON died on December 7 at Victoria, Vancouver Island, after a long illness, aged 73. He was the third son of the late R. B. Worthington, of Tonbridge. He went up to Caius College, Cambridge, with a considerable schoolboy reputation both as a cricketer and a footballer. He did, in fact, play as a forward several times for the university at rugby football, but missed getting his blue; he was, perhaps, unlucky to be up when Cambridge had a plethora of remarkable forwards—in one year every man in the Cambridge pack got an international cap while still in residence, and even one other for whom there was no room in the side that played Queen's. After taking his degree in 1899 "Bun" Worthington, as he was always known, entered St. Mary's Hospital. But almost at once the South African war began, and he volunteered for service in the Cambridge University contingent which served with the 1st Battalion, Suffolk Regiment. On return from service abroad he graduated B.Ch. in 1903 and was appointed to the Colonial Medical Service and posted to Nigeria. At that time the Colonial Service was very short of personnel, and he found himself at a station where he was not only medical officer but commander of the garrison and judge rolled into one. It fell to his lot to try a murderer; having condemned the man to death he then had to be sheriff as well and to supervise the execution. This decided him to try something else, so he resigned and took a commission in the R.N. Medical Service. After about 10 years he left this service and settled at Vancouver Island; but almost at once the war of 1914 broke out, and he became a captain in the C.A.M.C. Here, as in South Africa, his imperturbable cheerfulness and soldierly qualities made him extremely popular. He returned to Canada, and had lived at Nanaimo, B.C., in retirement for some years before his death.

Dr. EDWARD JAMES DAVIS-TAYLOR died very suddenly on December 29 at his home in Southsea, aged 76. He was the son of James Davis-Taylor, of Twerton-on-Avon, near Bath. From Bath College he went up to Caius College, Cambridge, where he was one of a celebrated crew which won the University Light Fours in 1895 and the Visitors' Cup at Henley in 1896. The four oarsmen all went to St. George's Hospital, where not unexpectedly they won the inter-hospitals rowing race: the other members were Dr. Drury Pennington and the late Dr. Gilbert Orme and Dr. H. H. Stiff. Davis-Taylor was spare man for the Cambridge eight of 1896, and got his Blue in 1897. He was of exceptionally powerful physique, and, like many other men of great strength, was very easy-tempered: to dressers, clerks, and his juniors in general he was always known as "Daddy"—than which no man could desire a better testimonial. He qualified in 1901, graduating M.B., B.Chir. three years later. After filling the usual house appointments at St. George's he became obstetric registrar there, and after that medical registrar and clinical medical tutor. He then started in general practice in Southsea, where he became physician to the Royal Portsmouth Hospital and to St. Andrew's Home for Children, as well as consulting physician to the Queen Alexandra Hospital, Cosham, to the Gosport Hospital, and to the Portsmouth Pensions Board. In the 1914–18 war he reached the rank of lieutenant-colonel in the R.A.M.C.T., and was mentioned in dispatches. Afterwards he was a military member of the Hampshire Territorial Force Association. Davis-Taylor was a member of the B.M.A. for many years: he was chairman of the Portsmouth Division in 1922–3 and secretary in 1924–5. He was also a vice-president of the Section of Neurology and Psychological Medicine at the Annual Meeting of the B.M.A. in 1923. In 1938 he had a serious breakdown in health, after which he was constrained in 1939 to retire from general practice, but was able to continue work through the recent war on medical boards and at the Queen Alexandra Hospital; this latter appointment he resigned as recently as 1949. He married Madeleine de la Salle in 1906: she died in 1940, leaving one son, who survives. Davis-Taylor was a highly educated general practitioner who understood enough of most specialties to be of real help to all his very large circle of patients. Although in greatest demand as a physician, he was well up in surgery as well—an all-rounder of a type which the modern tendency to specialization has rendered increasingly rare.

Dr. CHARLES WILLIAM GURD died in Belfast on January 11, aged 34. He was born in 1916, and educated at the Belfast Royal Academy, where he was head prefect. Proceeding to Queen's University with a leaving scholarship, he entered the faculty of science in 1935, and one year later transferred to the faculty of medicine. In his second year he won the much-coveted Symington Medal in anatomy, and took first scholarship in his year at the second professional examination. In his third year he also won a scholarship, and he graduated M.B., B.Ch. in 1941. During his period as a house-surgeon at the Royal Victoria Hospital Gurd's health broke down, but years of invalidism and several major operations did not damp his determination to resume useful work. After several years of inactivity he was enabled to take up the post of registrar to the skin department at the Royal Victoria Hospital, and he held the post of senior registrar when his life came to a sudden end from an acute heart attack after a bout of influenza. Those who worked with him and knew him well will long remember his tall handsome presence and his friendly smile. Deep sympathy will be felt with his wife, mother, and a brother in the R.N. Medical Service.

Medico-Legal

CHILD KILLED BY COUGH LINCTUS

At a recent inquest a boy aged 3 was found to have died after drinking a large quantity of "physeptone" linctus. This is a proprietary preparation containing 2 mg. per fluid drachm (3.5 ml.) of amidone hydrochloride, a drug covered by the Dangerous Drugs Acts. The linctus had been prescribed for the boy's father, who had used about half of it.

According to the mother's evidence she came into the living-room one morning, saw the medicine bottle nearly empty on the table, and vomit on the floor. She realized what had happened, and put her finger down her son's throat to make him sick, but he did not vomit again. Two and a half hours later her son became drowsy. Her doctor had him admitted to hospital immediately, but he died there early the next morning.

The pathologist who conducted the post-mortem examination gave the cause of death as poisoning due to ingestion of physeptone linctus,[1] adding that the normal adult dose of physeptone was 2 to 5 mg., while the child appeared to have taken 7 or 8 times that amount. At necropsy, the pupils showed very marked dilatation; the brain showed acute congestion and oedema; the pericardial sac contained a slight excess of clear yellow fluid; the heart was dilated, but otherwise normal; each pleural sac contained a trace of free fluid; and the lungs showed fairly extensive areas of collapse and marked congestion. There was no gross lesion in the gastro-intestinal tract, and liver, spleen, and kidneys were normal. Physeptone was found in the stomach washings.

The manufacturers of physeptone linctus have sent a letter to doctors indicating that patients should be warned against taking excessive doses of the linctus and against leaving bottles of it within the easy reach of children.

[1]*Coventry Evening Telegraph*, December 11, 1950.

Universities and Colleges

UNIVERSITY OF OXFORD

In Convocation on January 18 the honorary degree of D.C.L. was conferred on the Rt. Hon. Sir Godfrey Martin Huggins, P.C., C.H., K.C.M.G., F.R.C.S., Prime Minister of Southern Rhodesia.

P. D. Oldreive (Newport High School for Boys, Mon.) and R. P. Golding (Bristol Grammar School) have been elected to Nuffield Scholarships in Medicine at Pembroke College and Worcester College respectively.

UNIVERSITY OF CAMBRIDGE

Discussions on "The Relation of Pathology with Radiotherapy" will be held in the Department of Pathology of the University at 5 p.m. on the third Wednesday of each month and will be opened by Professor J. S. Mitchell and Dr. A. M. Barrett. The discussions are open, without fee, to all members of the University and to others who are interested in the subject.

Applications for the Gwynaeth Pretty Studentship, of the annual value of £250, tenable for three years, and the Nita King Scholarship of the annual value of £100, tenable for three years, must reach Professor H. R. Dean, M.D., F.R.C.P., Department of Pathology, University of Cambridge, before May 1. Full particulars may be obtained on application to Professor Dean. The holder of the studentship must devote himself to whole-time study and training for research in the aetiology, pathology, or treatment of disease with particular, but not exclusive, reference to those diseases which cripple or disable in childhood or early life. The holder of the scholarship shall devote himself to whole-time study and training for research in the aetiology, pathology, and prevention of fevers. The studentship may be held with the scholarship.

The W. A. Meek Scholarship, the emolument of which is £250, is open to candidates who propose to undertake research in any branch of study which comes within the scope of a number of faculties of the university, including Biology "A," Biology "B," and Medicine. The Amy Mary Preston Read Scholarship (emolument £150) is open to candidates eligible for the W. A. Meek Scholarship. Any graduate of the university is eligible for these scholarships, which are tenable for one year, provided his age on January 5, 1951, did not exceed 28 years. Applications must reach the Registrary of the University of Cambridge by February 13.

UNIVERSITY OF ST. ANDREWS

The degree of M.D. (with commendation) has been conferred upon K. R. Keay.

The following candidates have been approved at the examination indicated:

FINAL M.B., CH.B.—J. D. Adam, W. M. Anderson, A. A. Brand, V. W. M. Francis, R. J. D. Gibson, Elizabeth H. Halliday, W. Kelso, W. D. Lobban, D. MacDonald, Ida V. MacDonald, T. G. Sprunt, R. A. Yorston.

UNIVERSITY OF GLASGOW

The following medical degrees were conferred on January 13:

M.D.—H. E. Hutchison (with honours), A. G. McCarey, A. N. McPhail (with commendation), F. A. Smith.

M.B., CH.B.—J. I. Adam, W. D. Alexander, W. L. Birrell, Phyllis J. Bishop, A. H. Cassels, G. Church, D. W. Clementson, Betty Cowan, E. A. Cresswell, Margaret J. Croall, G. M. Davidson, Margaret J. Devine, K. Donald, I. B. R. Duncan, G. P. A. Evans, A. S. Ferrie, I. H. Gardner, J. M. B. Garland, D. H. Goold, H. Graham, J. H. Grant, Theresa Grant, A. Harrow, J. H. Henderson, T. J. G. Howie, G. A. Jamieson, R. D. Laing, J. D. Leonard, G. Lochrie, G. Y. McCririck, R. W. D. Macdonald, M. McEwen, N. P. Mackay, E. D. Mackie, Letitia S Macleod, J. L. McPheat, Frances I. Melrose, I. A. Millar, D. B Miller, M. E. Mowee, J. Owens, T. G. Parker, W. J. Patterson, T. C. Peden, Elizabeth Primrose, D. J. Reilly, M. J. Scott, J. D. A. Shedden, D. D. G. Simpson, J. G. Stewart, D. H. Sutherland, T. Taylor, N. A. Todd, G. R. Veitch, Marion M Whitelaw.

UNIVERSITY OF EDINBURGH

The ninth Sharpey Schafer Memorial Lecture will be delivered by Professor A. V. Hill, F.R.S., in the Anatomy Lecture Theatre, University New Buildings, Teviot Place, Edinburgh, on Friday, February 9, at 5 p.m. His subject is "The Physical Analysis of Events in Muscular Contraction." All interested are invited to attend the lecture.

UNIVERSITY OF LONDON

Professor J. M. Mackintosh has been appointed to represent the University at the Health Congress of the Royal Sanitary Institute to be held at Southport from April 23 to 27.

The following have been appointed, or nominated for appointment or reappointment, as representatives of the University on the governing bodies of the institutions indicated in parentheses: Professor J. M. Mackintosh (London School of Economics); Sir Francis Fraser (London School of Hygiene and Tropical Medicine Board of Management); Mr. P. H. Mitchiner and Professor A. A. Moncrieff (London School of Hygiene and Tropical Medicine Court of Governors); Mr. P. H. Mitchiner or Mr. J. B. Hunter (Royal Dental Hospital of London School of Dental Surgery); Dr. Ian Anderson (Canadian Red Cross Memorial Hospital, Taplow).

For the purposes of the M.D. examination, Branch I (Medicine), the following appointments have been approved: House-physician at St. James's Hospital, Leeds, and registrar; medical registrar (intermediate grade); junior registrar; house-physician at the Whittington Hospital, Highgate, London, N.

A Special University Lecture on "The Adrenocorticotrophic Hormone of the Pituitary Gland" will be delivered by Mr. C. J. O. R. Morris, Ph.D., M.Sc., in the Meyerstein Lecture Theatre, Westminster Medical School, Horseferry Road, London, S.W., on Tuesday, February 13, at 5 p.m. The lecture is addressed to students of the university and to others interested in the subject. Admission is free, without ticket.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examination indicated:

M.B., CH.B.—*Part III:* A. B. Anderson, Dorothy F. M. Burnett, R. W. H. Clarke, F. J. Deakin, C G. H. Hall, J. C. Hinchcliffe, J. A Howe, D. O. Hughes, P. Hughes, H G. McDonald, Roma MacDonald, C. McNamara, Alice N. O'Brien, Marianne A. A Phillips, J. A. Seddon, V. R. Tindall, A. Unsworth, T. D. Williams, R. G. B. Willis, D. Winter, M. C. Winter.

UNIVERSITY OF BRISTOL

The following candidates have been approved at the examinations indicated:

FINAL M.B., CH.B.—R. M. Barnes, Marianne A. Barry, Monica B. Bishop, K. A. Boulton, L. Epsztejn, B. R. W. Evans, Hella R. Fluss, R. F. Harvey, M. E. Hincks, K. R. Kidd, G. A. Pilkington, J. F. Rowland, Rachel D. R. Sasieni, Mildred M. C. Shaw, D. T. I. Stuttaford, Ginette M. Tebbutt, P. A. Titterton, Patricia Vowles. *In Group I (completing the examination):* H. Maxwell. *In Group II only:* R. E. D. Simpson.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—*Part II:* J. A. Ardis, K. W. Aron, E. C. Turton.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College, held on December 14, with Professor Ernest Finch, Vice-president, in the chair, the Council received from Viscount Nuffield a portrait of himself by Mr. John Wheatley, A.R.A.

The death of Mr. Neil Sinclair, past member of the Court of Examiners, was reported, and the Council unanimously approved a resolution of condolence.

The following were elected to the Fellowship of the Faculty of Anaesthetists: M. H. Davison, F. K. Boston, C. H. Budd.

The chairman reported that the annual meeting of Fellows and Members had been held on the previous day, when the annual report had been approved and a helpful discussion had taken place on the financing of the enlarged College of the future and the help which could be given by Fellows and Members.

Professor Finch was appointed Bradshaw Lecturer for 1951 and Mr. W. R. Le Fanu, Thomas Vicary Lecturer for 1951.

Sir James Paterson Ross was reappointed as the representative of the College on the National Association for Mental Health, Mr. R. P. Scott Mason on the Court of Governors of Birmingham University, and Mr. J. B. Oldham on the Court of Governors of the University of Liverpool.

Diplomas of Fellowship of the College were awarded as follows: J. H. Armstrong, W. M. Owen, J. H. Dobree, J. G. Jamieson, C. A. G. Cook, G. D. Cribb, L. C. L. Gonet, O. C. Fung, A. Katz, P. H. Tasker, B. J. Fowler, H. N. Reed, M. R. Thompson, E. C. Glover, J. W. F. Richardson, J. T. M. C. Jenkins, R. T. Routledge, J. C. Ballantyne, A. J. Partridge, E. S. Perkins, J. K. Wright, H. H. Bentall, L. G. Kingdom, C. W. S. F. Manning, W. K. Douglas, J. R. Moffat, C. R. McD. Redwood, M. B. Devas, W. E. J. Bennett, L. S. A. Boothroyd, R. W. L. Hurt, P. S. London, E. L. Trickey, W. A. Ashford Hodges, K. Owen, R. H. Shephard, D. E. E. Jones, D. O'Keeffe, W. H. Davies, A. R. Calo, C. J. L. Misso, A. T. Watson, P. R. Das Gupta, M. A. Abdallah, A. I. L. MacDiarmid, R. T. Burkitt, T. S. Jairam, T. A. R. Dinning, R. Dobson, A. H. Foate, W. B. N. Bomford, H. N. Burwell, T. L. Carr, S. L. Citron, C. E. A. Cragg, J. E. M. Dutton, J. H. Johnston, B. K. Mukherji, V. Rasanayagam, A. J. Spence, W. M. Walker, D. S. Eldin, J. W. Graham, C. R. Helsby, R. S. B. Hudson, J. B. Lynch, I. A. McGregor, A. Nizami, I. F. Potts, W. J. W. Sharrard, J. Siegler, M. Singer, J. C. Taylor, G. T. Watts, H. J. Wright, G. R. Anderson, G. S. Gunter, D. G. Hurley, J. W. Jackson, P. G. Jones, C. R. Neve, J. Oldfield, T. P. S. Powell, H. J. Shaw, T. V. Simpson, W. N. Gilmour, R. P. Hewitson, E. M. Kupfer, Wendy E. Lewington, J. K. Madan, J. H. Seymour, C. J. Windsor, J. Crossley, O. R. Nicholson, K. C. Mahajan.

The following hospital was recognized under paragraph 23 of the Fellowship regulations for the posts specified: Harlow Wood Hospital, Mansfield (registrar and two junior registrars, for six months)

At a meeting of the Council of the College, held on January 11, with Sir Cecil Wakeley, president, in the chair, Dr. William Kelsey Fry was congratulated on receiving the Honour of Knighthood in the New Year Honours List.

It was decided to institute a Department of Pharmacology at an early date.

Regulations were approved for the Joseph Henry Lectureship in Occupational Surgery.

The Council received with gratitude the following gifts: From Lady Lett, a portrait by James Gunn of Sir Hugh Lett, past president of the College; from Mr. V. M. Coppleson and other Fellows of the College in Australia, a replica of the Master's Chair of the Company of Surgeons which was destroyed by enemy action; from Sir Henry Cohen, a replica of the Robert Kelly Medal of the University of Liverpool.

Diplomas in Tropical Medicine and Hygiene, in Psychological Medicine, in Laryngology and Otology, in Medical Radiodiagnosis, in Medical Radiotherapy, in Anaesthetics, and in Industrial Health were granted, jointly with the Royal College of Physicians of London, to the following successful candidates:

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—E. G. R. Butler, A. M. Khan, A. Reyes, N. Sen, C. G. F. Smartt, G. A. Smith.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—A. A. Aziz, Ann Bolton, S. Brest, T. S. Davies, C. C. Evans, E. F. B. Forster, S. E. Hamid, H. B. Jones, D. M. Leiberman, A. M. Shenkin, K. Singh, C. A. Storr, R. Warnecke, J. Zelmanowits.

DIPLOMA IN LARYNGOLOGY AND OTOLOGY.—V. D. Bear, Betsy Brown, G. N. Dar, J. Freeman, A. E. W. Gregson, A. J. Gunning, H. S. A. Henry, D. G. H. Hollis, W. P. F. Kearney, Isabella Kingan, P. W. E. Moore, A. Nizami, K. R. Ogilvie, P. B. O'Neill, D. Singh, C. W. Smith, J. R. Watson.

DIPLOMA IN MEDICAL RADIO-DIAGNOSIS.—J. Adam, C. Allen, A. Attwood, J. Barr, S. Bose, A. W. Box, G. A. Burfield, D. E. Fletcher, A. J. M. Griffiths, K. E. Jefferson, A. W. R. Jenkins, J. R. Kirby, J. K. McMyn, C. P. Moxon, O. N. Saxena, H. K. Sen, R. M. S. Terry, P. W. Wishart.

DIPLOMA IN MEDICAL RADIOTHERAPY.—J. W. Boland, E. T. Feldsted, A. M. Goldstein, N. D. M. Harvey, M. Ramzan.

DIPLOMA IN ANAESTHETICS.—F. Alberts, B. P. Armstrong, H. I. O. Armstrong, F. Bakhshayesh, Kathleen Blott, R. C. Brown, H. Collier, L. F. G. Cruickshank, Sylvia Danks, Phyllis M. de Saram, F. G. Domaingue, J. R. Elliott, J. R. Forsaith, Beryl M. Goetzee, J. A. Griffiths, G. C. A. Jackson, P. S. Jenkin, E. L. Littler, P. L. McGwinn, L. V. Martin, Joan C. Mason, G. Mason-Walshaw, R. A. Nabi, Catherine E. D. Nash, H. G. Neill, D. M. O'Donoghue, Maureen O'Driscoll, J. J. Polland, Marjory A. Pollock, D. R. Rigg, A. R. Ryan, R. C. O. Saunders, E. R. Sinton, Elisabeth B. Smith, M. Spence, R. J. Vale, H. P. Varma, G. J. G. M. Vourc'h.

DIPLOMA IN INDUSTRIAL HEALTH.—M. M. Lewis, I. S. Maclean, H. T. Phillips, R. K. Phillips, A. W. Smith, J. L. Walsh.

A Diploma of Child Health was granted to Emily M. Frazer.

The following hospitals were recognized under paragraph 23 of the Fellowship regulations: Chelmsford and Essex Hospital (for one year, registrar; for six months, two house-surgeons, one orthopaedic house-surgeon); Harold Wood Hospital (for six months, junior surgical registrar, two house-surgeons, one orthopaedic house-surgeon); Norfolk and Norwich Hospital (ear, nose, and throat house-surgeon); Orpington Hospital (for six months, one registrar and two house-surgeons (general surgery), one registrar and one house-surgeon (orthopaedic)); Queen Mary's Hospital, Sidcup (till December 31, 1951, resident surgical officer, two house-surgeons (all for six months)); Kogarah, New South Wales—St. George's Hospital.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At a meeting of the Royal College of Surgeons of Edinburgh held on December 20, 1950, with Mr. W. Quarry Wood, president, in the chair, the following candidates, having passed the requisite examinations, were admitted Fellows: S. D. Bharucha, R. A. Bremner, L. Bryer, J. C. Campbell, M. L. Chatterjee, W. Y. Cornock, M. F. El Giziri, T. G. Evans, R. H. Freeman, D. McA. Hancock, W. T. Irvine, G. Krishna, R. Lipschitz, G. McIntosh, J. T. Marcroft, A. R. Murison, J. R. Reid, E. G. Sarofim, A. Schuller, B. M. C. Sedzimir, T. V. Simpson, P. C. Steptoe, A. B. M. Stevenson, F. Viedge, T. Visvanathan, C. J. Windsor.

ROYAL COLLEGE OF SURGEONS IN IRELAND

On June 12, 1952, the President and Council of the College will adjudge prizes of £150 and £100 for the best essays presented to them for the Carmichael Prize Essay. Candidates are required to submit essays in accordance with the following instructions: (1) The state of the medical profession in its different departments of physic, surgery, and pharmacy, in Great Britain and Ireland, at the time of the writing of these prize essays. (2) The state of the hospitals and schools of medicine, surgery, and pharmacy. (3) The state and mode of examination, or of testing the qualifications of candidates of the different licensing Colleges or Corporations of medicine, surgery, and pharmacy. Full particulars may be obtained from Professor Norman Rae, Sc.D., Registrar, Royal College of Surgeons in Ireland, 123, St. Stephen's Green, Dublin, Eire, to whom essays must be sent by February 1, 1952.

The following candidates have been approved at the examinations indicated:

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—E. R. Jones, W. A. MacIlrath.

DIPLOMA IN ANAESTHETICS.—A. MacA. Blayney, J. T. Bolger, F. MacD. Byrne, C. F. Cunniffe, R. I. Dixon, Sylvia Pescatori.

DIPLOMA IN CHILD HEALTH.—J. R. Barua, Elizabeth Harpur, S. M. A. Khadri, Susan O'Connell, F. A. Patel, Rose Shields.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending January 6 (No. 1).

Figures of notified *cases* are for: (*a*) England and Wales (London included) (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending January 6					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	38	5	11	4	6	75	12	23	6	4	1,027	439	75
Deaths	2	—	—	—	—	—	—	—	—	—			
Dysentery	834	74	98	3		199	17	54	—	—	285	119	65
Deaths		1		—					—				
Encephalitis, acute	4	2	—	—		4	—	—	—	—	4	1	—
Deaths		—			1		—						
Erysipelas			17	2	7			34	7	13			
Food-poisoning	108	33		—		49	10		—				
Infective enteritis or diarrhoea under 2 years				8	12					14			
Deaths	19		2	2	2	27	1	7	1	8			
Measles*	21,688	2,753	75	65	130	2,337	43	12	219	85	14,210	3,746	569
Deaths		2	—	—	1			—	—	—			
Meningococcal infection	50	4	26	2	2	39	5	21	—	—	149	53	38
Deaths		—	2				1	1					
Ophthalmia neonatorum	26	—	13	—		46	2	12	3	—	101	63	46
Pneumonia, influenzal	1,774	109	28	20		1,120	72	19	17	4	1,617	1,165	975
Deaths (from influenza)†	458	40	17	8	1	52	7	3	—	—			
Pneumonia, primary			431					408					
Deaths	770	111		31	16	299	66		6	21			
Poliomyelitis, acute:													
Paralytic	37	4	2	—	3	54	1	1	1	5	50	10	3
Non-paralytic	10	—											
Deaths§	3	—			—	10	1			1			
Puerperal fever			3				—	7	—				
Puerperal pyrexia‖	90	6	9	1	1	97	5	6	—	—	166	124	73
Scarlet fever	923	59	174	36	82	1,798	122	255	178	89	1,808	1,462	963
Deaths		—	—	—	—			—	—	—			
Smallpox	13	—	—	—		—	—	—	—	—			
Deaths				—					—				
(1) Tuberculosis, respiratory			94	30				131	26				
(2) Tuberculosis, non-respiratory			15	9				22	—				
(1) Deaths	245	37	38	9	15	201	30	31	9	8			
(2) Deaths		1	5	1	3		1	2	1	2			
Typhoid fever	4	2	1	—	3	28	1	—	—	3			
Deaths¶	—	—	—	—		—	—	—	—		31	9	5
Paratyphoid fever	1	—	1 (B)	—		3	1	—	—	—			
Whooping-cough	5,009	521	442	25	64	1,379	61	147	50	41	2,306	1,679	1,048
Deaths	12	1	1	—	3	3	—	—	1	—			
Deaths (0–1 year)	334	51	51	16	17	289	46	65	10	29	612	425	289
Deaths (excluding stillbirths)	9,860	1,570	1,053	256	284	5,631	935	720	137	214	6,820	6,084	5,091
Annual death rate (per 1,000 persons living)			21·2					14·4					
Live births	6,858	1,217	903	231	320	7,364	1,266	943	255	391	10,881	7,542	5,331
Annual rate per 1,000 persons living			18·1					18·9					
Stillbirths	173	20	17			180	31	28			336	224	180
Rate per 1,000 total births (including stillborn)			18					29					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

EPIDEMIOLOGICAL NOTES

Influenza

The outstanding features of the statistics for England and Wales for the week ending January 13 are:

(*a*) The considerable increase in the great towns of influenza deaths to 890, the largest increment in the last 20 years.

(*b*) The occurrence of the bulk of this increase in influenza deaths in the Northern and North-western regions, as indicated in the following summary:

	Week Ending January 6	Week Ending January 13
Northern	83 per million	91 per million
N. Western	63 „ „	138 „ „
London and S.E.	11 „ „	21 „ „
Remaining regions average..	5 „ „	13 „ „

(*c*) The limitation of influenza deaths to the older age groups, 85% being over 55 years.

(*d*) Increase of the pneumonia cases and deaths in the great towns but proportionately much less than that of influenza deaths.

(*e*) Limitation of large numbers of deaths from pneumonia and influenza to the great towns in the more northerly regions of the country and especially Liverpool, which suffered out of all proportion to any of the other great towns.

(*f*) A rise in weekly claims in the Ministry of National Insurance to a record height of 412,000 in the week ended January 9.

There is a prevalence of influenza in Finland, cases of which have been shown to be due to the A prime strain. From Spain there is evidence of the disease being due to virus A. This has also been established as regards the Dutch outbreak.

The following cases of and deaths from pneumonia and influenza in the great towns have been reported:

	11/11	18/11	25/11	2/12	9/12	16/12	23/12	30/12	6/1	13/1
Pneumonia:										
Cases ..	261	313	302	282	347	374	364	502	956	1,300
Deaths ..	177	188	207	198	236	289	351	383	770	982
Influenza:										
Deaths ..	20	16	24	28	34	33	54	102	458	890

Totals from the first week of the year in the great towns compared with the preceding two years are as follows:

	1949	1950	1951
Pneumonia:			
Cases	1,237	1,189	2,256
Deaths	799	599	1,752
Influenza:			
Deaths	87	99	1,348

The following Table shows notifications of pneumonia—primary and influenzal—in England and Wales:

	11/11	18/11	25/11	2/12	9/12	16/12	23/12	30/12	6/1	13/1
Pneumonia..	465	558	490	497	573	684	647	962	1,774	2,538
Corresponding week, 1949-50	534	667	710	715	734	676	634	842	1,120	991

The deaths cannot be related to the cases in these Tables.

Regional totals of influenza deaths in the great towns in the week ending January 13 and rates per million (in parentheses) were: Northern 113 (91.1), East and West Ridings 34 (14.3), North Western 497 (137.6), North Midland 16 (15.25), Midland 34 (14.8), Eastern 20 (26.6), London and S.E. 146 (20.7), Southern 12 (14.6), South Western 14 (14.5), Wales 4 (6.0).

Influenza deaths in the great towns by age groups were: Under 1, 12; 1–15, 4; 15–25, 3; 25–35, 7; 35–45, 33; 45–55, 75; 55–65, 156; 65–75, 277; 75 and over, 323; all ages, 890.

The following Table shows the great towns with the largest numbers of influenza and pneumonia deaths for the week ending January 13:

	Total Deaths	Deaths from (*a*) Influenza	Deaths from (*b*) Pneumonia	Deaths from (*a*) and (*b*)
Gateshead ..	81	11	18	29
Middlesbrough ..	93	12	14	26
Newcastle ..	194	31	22	53
Sunderland ..	111	17	16	33
West Hartlepool..	52	12	13	25
Leeds	164	13	22	35
Birkenhead ..	168	42	14	56
Liverpool ..	949	216	214	430
Manchester ..	384	10	21	31
St. Helens ..	130	15	5	20
Wallasey	180	50	19	69
Bristol	189	6	14	20
Blackpool.. ..	97	14	19	33
Southport ..	75	15	5	20
Warrington ..	81	19	8	27
Birmingham ..	360	12	21	33
Greater London ..	3,297	173	273	446

Influenza Epidemics

The level of influenza mortality in the last few years has undergone considerable change, and the recent death rates have been lower than any recorded in the 50 years preceding 1940. Influenza epidemics for the 20 years following the pandemic of 1918–19 appeared to follow a 2- to 4-year cycle. Since 1929, when the largest recorded epidemic apart from the 1918–19 pandemic occurred (29,084 deaths were registered in England and Wales in this year from influenza), the epidemic level of influenza has steadily fallen accompanied by a fall in the inter-epidemic death rates. The last outbreak of influenza with a death rate of over 300 per million occurred in 1943. Since 1943 the annual death rate has fluctuated between 29 per million in 1948 and 130 in 1946.

This change in the level of influenza mortality has been accompanied by variations in the seasonal trend of the deaths. Before 1944 the numbers of deaths from influenza in the great towns began to rise at the beginning of the year and generally reached a maximum towards the end of the first quarter. The outbreak expected in 1944 started about two months earlier than usual, and the numbers of deaths began to rise in the 46th week of 1943, reaching a maximum of 1,148 in the 49th week. The deaths then fell rapidly and the outbreak was notable only for its appearance in time. In 1948 the rise in influenza mortality failed to appear for the first time, and the largest weekly number of deaths recorded in the great towns was only 35. In the present year the outbreak of influenza has again departed from the customary pattern by appearing about a month early, resembling the outbreak of 1943. The numbers of deaths recorded in the great towns in the first and second weeks of the year were 458 and 890; these are the largest weekly totals since the outbreak of 1943.

It would be rash to attempt to predict the course of the present epidemic in view of the changing trend of influenza, but with such an early rise it is probable that a large outbreak will develop. The deaths from influenza in the large towns during the peak period for recent years are as follows:

Week	1945–6	1946–7	1947–8	1948–9	1949–50	1950–1
49	35	21	23	24	23	34
50	69	22	15	24	41	33
51	76	26	20	25	27	54
52	72	33	35	29	28	102
1	123	36	23	47	52	458
2	166	74	13	40	47	890
3	174	85	18	45	39	
4	273	92	24	37	47	
5	297	148	15	64	61	
6	304	211	16	94	80	
7	220	163	27	158	76	
8	141	135	20	251	78	
9	123	121	27	259	76	
10	112	92	31	321	108	
11	94	80	20	360	167	
12	77	66	14	327	135	
13	52	38	15	274	121	
14	48	29	9	192	117	
15	26	33	10	95	56	

Smallpox at Brighton

Up to noon on January 22 there had been no notifications of smallpox outside the Brighton area. The total number of cases notified (uncorrected) is 30, and there have been 9 deaths. With two exceptions the recent cases have occurred in contacts under surveillance. It would be premature to state that all the sources of infection in Brighton are known or that the end of the outbreak can be foreseen. The need for special vigilance continues throughout the country.

Poliomyelitis

Notifications in the week ending January 13 were: paralytic, 27 (37); non-paralytic, 11 (10); total, 38 (47). There were thus 9 fewer notifications compared with the previous week, for which the figures are given in parentheses. Notifications in the corresponding week of the previous four years were: 1947, 16; 1948, 49; 1949, 37; 1950, 50.

The notifications in the second week of 1951—38—are therefore well below those for the corresponding week in 1948 and 1950. These three years are comparable in that they followed years of very high prevalence of the disease.

Infectious Diseases

During the first week of the year large increases were recorded in England and Wales in the number of notifications of measles 4,220, whooping-cough 1,319, acute pneumonia 812, and dysentery 143. The notifications of acute pneumonia were the largest recorded since the early weeks of 1941. Measles is very prevalent, and the number of notifications was the largest ever recorded, being 1,542 more than the previous high level recorded for the eighth week of 1943. The largest rises for measles during the first week of the year were London 831, Yorkshire West Riding 641, Essex 417, Nottinghamshire 363, Lancashire 285, Middlesex 276.

The number of notifications of whooping-cough has been exceeded only in one previous outbreak. The highest level of whooping-cough was attained in the 26th and 27th weeks of 1941, when 5,453 and 5,324 cases were notified. The largest rises during the week occurred in London 196, Staffordshire 137, and Essex 111. The incidence of diphtheria remains low, and is only half the level of a year ago. The chief feature of the recent returns of diphtheria is the small but persistent outbreak in Birmingham C.B., where 62 cases have been notified in the last nine weeks. The notifications of acute poliomyelitis declined by six in the first week of the year; the largest returns were Devonshire 6, London 4, Staffordshire 4.

Dysentery

A rise was recorded in the notifications of dysentery during the first week of the year. This rise follows a decline lasting two weeks which terminated the eight-week consecutive rise in incidence from 169 cases in the 42nd week of last year to 1,214 cases in the 50th week. The largest returns during the week ended January 6 were: Leicestershire 141 (Leicester C.B. 105, Hinckley U.D. 15); Lancashire 109 (Southport C.B. 20, Liverpool C.B. 16, Manchester C.B. 14, Oldham C.B. 11, Middleton M.B. 10); London 74 (Westminster 33, Islington 13); Yorkshire West Riding 59 (Sheffield C.B. 13, Earby U.D. 11); Sussex 56 (Eastbourne C.B. 51); Salop 38 (Shrewsbury M.B. 26); Warwickshire 35 (Birmingham C.B. 31); Middlesex 31 (Edmonton M.B. 10); Staffordshire 27 (Cheadle R.D. 12); Cheshire 26 (Northwich U.D. 9, Nantwich R.D. 8); Southampton 24 (Southampton C.B. 20); Northamptonshire 24 (Kettering M.B. 19); Essex 24 (Romford M.B. 9); Surrey 23 (Croydon C.B. 13); Monmouthshire 21 (Newport C.B. 9, Abercarn U.D. 9); Kent 19 (Orpington U.D. 14); Glamorganshire 13 (Swansea C.B. 9); Wiltshire 11 (Marlborough and Ramsbury R.D. 10); Northumberland 10.

Week Ending January 13

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 852, whooping-cough 4,980, diphtheria 30, measles 18,658, acute pneumonia 2,538, acute poliomyelitis 38, dysentery 698, smallpox 11, paratyphoid fever 8. 890 deaths were attributed to influenza in the great towns.

Quarterly Returns for England and Wales

The birth rate during the September quarter of 1950 was 15.4 per 1,000 of the population, and was the lowest rate for a third quarter since 1941. The infant mortality was 24 per 1,000 related live births; this was the lowest rate ever recorded in this country, being 3 per 1,000 below that for the third quarter of 1949 and 14 below the average rate for the third quarters of the 10 preceding years 1939–48. Stillbirths had a rate of 22.3 per 1,000 total births, which was 0.3 above the rate for the third quarter of 1949. The general death rate was 9.3 per 1,000, being 0.1 above the rate for the corresponding quarter of 1949 and the same as the average for the third quarters of the five years 1944–8.

The corrected notifications of acute poliomyelitis were 3,200 paralytic and 1,431 non-paralytic cases; 373 deaths were attributed to this disease during the quarter.

An abridged life table for 1949 gave an expectation of life at birth as 66.01 years for males and 70.63 years for females. Compared with the English Life Table No. 10 (1931) these values show an increase of 7.27 years for males and 7.75 years for females.

Medical News

New Assistant Secretary for B.M.A.

The Council of the Association is to appoint a new assistant secretary (see our advertisement columns, page 18). Since Dr. A. Macrae succeeded Dr. Charles Hill, M.P., as Secretary the establishment of the Headquarters secretariat of eight has been one short. The closing date for applications, which should give full particulars of experience, qualifications, age, and the names of three referees, is February 14.

Lady Tata Memorial Trust

The trustees of the Lady Tata Memorial Fund invite applications from workers of any nationality for grants and scholarships for research on diseases of the blood, with special reference to leukaemia, in the academic year beginning October 1. Grants of variable amount are made for research expenses or to provide scientific or technical assistance for senior workers. Scholarships are intended chiefly to support junior investigators working under suitable direction; their normal value has been £400 per annum for whole-time research, with proportionate adjustment for work on a part-time basis, where this has been approved. Applications must be submitted before March 31, and the awards will be announced in June. Further particulars and forms of application may be obtained by writing to the secretary of the Scientific Advisory Committee, c/o Medical Research Council, 38, Old Queen Street, London, S.W.1.

Research in Vital Statistics

The World Health Organization has set up a centre for statistical research on problems arising in the use of the International Statistical Classification of Diseases, Injuries, and Causes of Death. It has appointed Dr. Percy Stocks, until recently chief medical statistician at the General Register Office, to direct its work. The centre is at the General Register Office, which is assisting by making available appropriate material from its records. Dr. Stocks will continue for the present to act as a consultant to the General Register Office.

Classification of Cervical Cancer

An Anglo-American committee representing various obstetric and gynaecological interests agreed in May last year to certain modifications of the League of Nations' Classification, 1937. The new version in summary reads: *Stage 0*, carcinoma *in situ* (pre-invasive carcinoma, intra-epithelial carcinoma); *Stage 1*, carcinoma strictly confined to the cervix; *Stage 2*, extends beyond cervix but has not reached pelvic wall, and the lower third of the vagina is not involved; *Stage 3*, carcinoma has reached pelvic wall; *Stage 4*, bladder and/or rectum involved. The main change is the introduction of Stage 0, created because, although the majority of gynaecologists will not accept as carcinoma cases diagnosed solely on the evidence of smears, in many of these cases biopsy shows a condition of "Cancer *in situ*" for which many feel it justified to perform a hysterectomy, at least in women past the menopause.

More News of Peckham

The people who used to be the patients of the Pioneer Health Centre at Peckham, lately purchased by the London County Council (*British Medical Journal*, December 30, p. 1503), have independently formed their own Peckham Centre Members' Association as a family club, and are now appealing to the Camberwell Borough Council and the L.C.C. for an unclaimed bombed site on which to build.

Distressed Gentlefolk's Aid Association

This society, which is over 50 years old, is appealing for funds to carry on its work of providing grants, pensions, clothes, and comforts, and in some cases a residential home, for distressed gentlefolk—i.e., people of similar education and interests. About 400 people are at present receiving grants, while about 73 are being maintained in the association's three homes. Last year's balance-sheet shows an expenditure of over £60,000. The address for donations and further information is 6, Iddesleigh House, Caxton Street, London, S.W.1.

King Edward's Hospital Fund

This fund disposes of some £300,000 annually, and is a voluntary body which does a great deal to help the hospital services both by direct financial and by administrative help and advice. The Emergency Bed Service is one well-known side of its work. The extensive costing survey being carried out on behalf of the Ministry of Health among London hospitals is another. In April it hopes to open a hospital administrative staff college. Eighty voluntary convalescent homes, representing 3,000 beds, have been materially helped, and good progress is being made with a £250,000 scheme started in 1949 to provide 12 homes for the aged sick. Nearly £20,000 in the past year has been allocated to National Health Service hospitals to provide necessary items which the State does not pay for. The Fund also issues reports and recommendations on such important subjects as hospital catering and the supervision of nurses' health.

North of England Obstetrical and Gynaecological Society

A meeting of the Society was held in Manchester on November 24, 1950. The president, Mr. H. Harvey Evers, was in the chair. Mr. J. A. Hadley and Mr. R. F. Lawrence described one case of advanced abdominal pregnancy, and an account of another, this time full-term, was given by Mrs. A. E. Marrow. Dr. E. E. Rawlings and Dr. R. Warwick described a case of conjoined twins, and Mr. D. C. Racker read a communication on the blood supply to the lower end of the ureter and its relevance to Wertheim's hysterectomy.

Egyptian Decorations

The King of Egypt has conferred the Order of El Maaref, Second Class, upon Professor D. E. Derry, M.C., and Dr. R. W. Haines in recognition of valuable services rendered by them at the Fouad I University, Cairo.

Girdlestone Scholarship

Lord Nuffield has donated £10,000 to the Nuffield Orthopaedic Centre, Oxford, for the purpose of creating a scholarship in memory of the late Gathorne Robert Girdlestone, founder of the Wingfield-Morris Orthopaedic Hospital and one time Nuffield Professor of Orthopaedic Surgery in the University of Oxford. It will be known as the Girdlestone Scholarship, and will enable doctors from overseas to spend a period of time at the Wingfield-Morris Orthopaedic Hospital working within, and learning from, the organization he created and which so clearly bears the imprint of his personality. Details of the scholarship will be announced later.

Memorial to C. J. Bond

At the Leicester Royal Infirmary on January 10 Professor Grey Turner unveiled a tablet in memory of C. J. Bond, who had served the institution as an active surgeon for 27 years and as a consulting surgeon until his death at 83 in 1939. At the Leicester Medical Society the same evening he delivered the first C. J. Bond memorial lecture.

In Brief

The council of the Royal Society of Medicine has awarded the W. J. Harrison Prize in Otology posthumously to the late Mr. John Gerrie, formerly chief aural surgeon to Aberdeen Royal Infirmary.

Dr. Jacqueline Walker has been appointed acting director of the Mycological Reference Laboratory, London School of Hygiene and Tropical Medicine, London, W.C.1, which is part of the Public Health Laboratory Service.

Wills

Dr. Roderick Macleod, of Durham, formerly medical officer of health for Hetton U.D.C., left £11,547; Dr. W. J. S. Bythell, of Bridgnorth, £14,026; Dr. William Guy, formerly Dean of the Edinburgh Dental Hospital and President of the British Dental Association, £6,355; Dr. S. R. Gleed, of Finchley, £19,807; Mr. P. L. Daniel, consulting surgeon to Charing Cross Hospital and the Gordon Hospital, £20,462; Dr. S. H. Greene, for 50 years in general practice in North Kensington, £8,211; Lieut.-Col. H. R. Dutton, I.M.S. (retd.), formerly Principal and Professor of Medicine, Prince of Wales Medical College, Patna, Bihar, and Orissa, India, £17,686; Lieut.-Col. W. R. Dawson, R.A.M.C. (retd.), late Chief Medical Officer of the Ministry of Home Affairs, Northern Ireland, £14,403; Dr. C. C. C. Court, of Ilminster, Somerset, £12,269; Dr. H. B. Lewers, of Ilfracombe, £15,854; and Dr. F. B. G. Holmes, of St. Annes-on-Sea, £43,625.

COMING EVENTS

Mental Health Conference

A conference on "Community Mental Health in Practice," arranged by the National Association for Mental Health, will be held at St. Pancras Town Hall, Euston Road, London, N.W.1, on Monday and Tuesday, March 12 and 13, beginning at 10 a.m. each day. Tickets and details may be obtained in advance from the conference secretary, 39, Queen Anne Street, London, W.1.

Milroy Lectures

Dr. J. C. Broom will deliver the Milroy Lectures before the Royal College of Physicians of London (Pall Mall East, S.W.) on Tuesday and Thursday, February 13 and 15, at 5 p.m. His subject is "Leptospirosis."

Third International Congress of Hygiene and Mediterranean Medicine

This will be held on May 14, 15, and 16 at Palermo, under the presidency of Professor Maurizio Ascoli. Full information may be obtained from Segreteria del III Congresso Internazionale d'Igiene e Medicina Mediterranea, Ufficio d'Igiene, Piazza Aragonezi, Palermo.

Chronic Rheumatic Diseases

A concentrated week-end course of lectures, ward rounds, and practical demonstrations is being held at the rheumatism unit of St. Stephen's Hospital, Chelsea, S.W.10, on Saturday and Sunday, March 3 and 4. Full details can be obtained on application to the medical registrar of the unit or from the College of Postgraduate Medicine, 1, Wimpole Street, W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

●INSTITUTE OF CHILD HEALTH, Hospital for Sick Children, Great Ormond Street, London, W.C.—January 29, 5 p.m., "*The Prevention of Tuberculosis in Childhood*," by Dr. B Thompson.

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, London, W.C.—January 29, 5 p.m., "*Some Recent Advances in the Neurophysiology of Vision*," by Professor H. Hartridge, F.R.S.

●ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—January 29, 5.30 p.m., "*Anatomy of the Eye and Orbit*," by Professor T. Nicol.

●SOCIETY FOR CULTURAL RELATIONS WITH THE U.S.S.R., 14, Kensington Square, London, W.—January 29, 8 p.m., "*Recent Controversies in Soviet Medical Theory Based on the Work of Pavlov, A. D. Speransky, Bykov, and O. B. Lepeshinskaya*," discussion to be opened by Dr. Leonard Crome, followed by Mr. D. R. Newth, Dr. J. S. Horn, and Mr. Roscoe Clark.

Tuesday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., January 30, 5.30 p.m., "*The Organization of Muscular Movements by the Cerebral Cortex*," by Dr. F. M. R. Walshe, F.R.S.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—January 30, 5 p.m., "*Lichen Planus and Lichenoid Eruptions*," by Dr. R. M. B. MacKenna.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—January 30, 5 p.m., "*Ocular Complications of Diabetes*," by Dr. T. H. Whittington.

Wednesday

EDINBURGH CLINICAL CLUB.—At Maternity Department, Western General Hospital, January 31, 4 p.m., clinical meeting by Dr. A. S. Duncan.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—January 31, 5 p.m., "*Medical Mycology*," lecture-demonstration by Dr. R. W. Riddell.

RENAL ASSOCIATION.—At Ciba Foundation, 41, Portland Place, London, W., January 31, 4.30 p.m., papers: "*Some Aspects of the Foetal Kidney*," by Professor E. C. Amoroso; "*The Neurohypophysis and the Kidney*," by Professor E. B. Verney; "*Certain Aspects of Tubular Function*," by Dr. Charles Dent. A discussion will follow.

Thursday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., February 1, 5.30 p.m., "*The Psychology of Personality*," by Mr. H. J. Eysenck, Ph.D.

FACULTY OF HOMOEOPATHY.—At Royal London Homoeopathic Hospital, Great Ormond Street, London, W.C., February 1, 5 p.m., "*Fears*," by Dr. Kathleen G. Priestman; "*A Short Proving of Strophanthus Sarmentosus*," by Dr. Mora A. C. O'Hanlon.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—February 1, 5 p.m., "*Leukoplakia: Lichen Sclerosus of the Ano-genital Region*," by Dr. H. J. Wallace.

LIVERPOOL MEDICAL INSTITUTION.—At Broadgreen Hospital, February 1, 3.30 p.m., afternoon clinical demonstration.

ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Materia Medica Department, Medical School, Small's Wynd, Dundee, February 1, 5 p.m., "*Some Considerations of the Pulmonary Circulation in Man*," by Professor W. Melville Arnott.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—February 1, 4.30 p.m., lecture-demonstration on neurology.

Friday

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—February 2, 8 p.m., Inter-debate with Glasgow University Medico-Chirurgical Society.

UNIVERSITY COLLEGE (Physiology Theatre), Gower Street, London, W.C.—February 2, 5.15 p.m., "*Cell Metabolism and Chemotherapeutic Activity*," by Mr. T. S. Work, Ph.D.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY, Whipps Cross Hospital, London, E.—February 2, 8.30 p.m., "*The Engineering Approach to Rehabilitation Within the Industry*," by Dr. A. R. Thompson.

APPOINTMENTS

ADAMS, MARY I., M.B., B.Ch., D.P.H., Medical Officer of Health, Metropolitan Borough of Fulham.

AINSLIE, D., M.B., B.Chir., F.R.C.S., D.O.M.S., Assistant Ophthalmic Surgeon (Consultant), Middlesex Hospital, London, W.

COWAN, NAIRN REID, M.D., D.P.H., D.I.H., Medical Officer of Health, Royal Burgh of Rutherglen.

HARRIS, D. W. T., M.R.C.S., L.R.C.P., D.P.M., D.P.H., Assistant (Deputy) County Medical Officer of Health, Breconshire County Council.

LIVERPOOL REGIONAL HOSPITAL BOARD.—W. R. Hunter, Ch.M., F.R.C.S., Consultant General Surgeon, Walton Hospital: G. H. Murray, M.B., Ch.B., M.R.C.P.Ed., Whole-time Consultant Chest Physician, North Liverpool Area.

NORTH-EAST METROPOLITAN REGIONAL HOSPITAL BOARD.—The following appointments at the hospitals indicated in parentheses are announced: *Full-time Pathologist* L. Steingold, M.B., Ch.B. (St. Andrew's, Bow). The following are part-time appointments: *Anaesthetists*, D. V. Bateman, M.B., B.Chir., D.A. (Haymeads and Bishops Stortford); F. E. Clynick, M.B., Ch.B., D.A., and B. Kenton, M.R.C.S., L.R.C.P., D.A., D.C.H. (Bethnal Green); H. Grenville, M.R.C.S., L.R.C.P., D.A. (London Jewish and St. Margaret's, Epping); G. Herington, M.B., B.S., D.A. (Wanstead). *Ear, Nose, and Throat Surgeon*, E. M. H. Foxen, F.R.C.S., D.L.O. (Enfield War Memorial). *Orthopaedic Surgeon* G. R. Fisk, F.R.C.S. (St. Margaret's, Epping). *Paediatricians*, T. R. Savage, M.R.C.P., D.C.H. (Oldchurch and Wanstead), I. G. Wickes, M.B., B.Chir., M.R.C.P., D.C.H. (South-east Essex Group). *General Physicians*, R. C. S. Benson, M.B., B.S., M.R.C.P. (Rush Green); A. Nelson-Jones, M.D., M.R.C.P. (Forest and Woodford Jubilee).

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—*Senior Hospital Medical Officer in Psychiatry to Mendip Hospital, Wells*: A. E. P. Swinson, M.B., B.Ch.; *Senior Hospital Medical Officer Anaesthetist to Southmead Hospital, Bristol*, W. J. Lewis, M.R.C.S., L.R.C.P., D.A.; *Senior Surgical Registrar in South Somerset Clinical Area*, H. H. W. Jackson, M.B., F.R.C.S.; *Senior Surgical Registrar in Bristol Clinical Area*, G. H. Darke, M.B., F.R.C.S.Ed.

WARNOCK, DOREEN G., M.B., Ch.B., D.P.H., D.R.C.O.G., Assistant Medical Officer, Maternity and Child Welfare Department, Aberdeen.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Barrowcliff.—On January 15, 1951, at Stratford-on-Avon, to Germaine (formerly Aquettant), wife of Dr. D. F. Barrowcliff, a son—Gregoire Duke Noel.

Craddock.—On January 15, 1951, at Alexandra Maternity Home, Devonport, to Paddy, wife of Dr. Denis Craddock, M.B., Ch.B., D.Obst.R.C.O.G., a son—Stephen John Hamilton.

Hogarth.—On January 16, 1951, at the London Clinic, to Harriette R. Lewis, wife of Dr. J. Clancy Hogarth, M.D., M.R.C.P., a son.

Lloyd Dawe.—On January 5, 1951, at the British Military Hospital, Singapore, to Stella (formerly Crain), wife of Edwin Lloyd Dawe, Captain, R.A.M.C., a daughter—Dorcas Helen.

McConnell.—On January 13, 1951, at Bristol, to Joan, wife of Dr. Brian McConnell, a son.

Minto.—On January 21, 1951, at Northampton, to the wife of Dr. W. H. P. Minto, a son.

MARRIAGES

Benn—Simpson.—On January 8, 1951, at Leicester, Joseph Benn, M.D., M.R.C.P., to Patricia Mary Simpson, M.B., Ch.B.

Diggory—McConnell.—On January 6, 1951, at Christ Church, Lancaster Gate, London, Peter L. C. Diggory, M.B., of Hereford, to Patricia McConnell, M.C.S.P., of Martin-in-Cleveland, Middlesbrough.

Smith—Heron.—On December 30, 1950, Mr. C. M. G. Smith, Trinity College, Cambridge, to Nancy Heron, M.B., Ch.B., D.Obst.R.C.O.G., Springsyde, Otley, Yorks.

DEATHS

Dyson.—On January 7, 1951, at Hemsworth, near Pontefract, Yorks, William Dixon Dyson, M.B., Ch.B., aged 51.

Franklin.—On January 7, 1951, at the Middlesex Hospital, London, W., Philip Franklin, F.R.C.S., of 11, Wimpole Street, London, W.

Gask.—On January 16, 1951, at Hambleden, Henley-on-Thames, George Ernest Gask, C.M.G., D.S.O., F.R.C.S., aged 75.

Greenwood.—On January 3, 1951, at Darlington, Alan Young Greenwood, M.D., of North Thornfield, Darlington.

Hall.—On January 3, 1951, at 342, Glossop Road, Sheffield, Sir Arthur John Hall, M.D., F.R.C.P., aged 84.

Hardy.—On January 4, 1951, at "Brackendale," St. George's Hill, Weybridge, Surrey, Francis Alexander Hardy, M.D., aged 78.

Irwin.—On January 4, 1951, at "Camlin," Nuns Walk, Wentworth, Virginia Water, John O'Malley Irwin, L.R.C.P.&S.I.&L.M., formerly of Tientsin, North China, aged 75.

Jones.—On January 4, 1951, Francis Grice Jones, M.B., C.M., of The Residence, Denbigh, North Wales, aged 88.

Kelly.—On January 7, 1951, at Grange View, Meols Drive, West Kirby, Thomas William Kelly, M.D., formerly of Luddenden, Yorks.

Lloyd.—On January 4, 1951, at his home, Milford-on-Sea, Hants, Robert Archer Lloyd, D.S.O., M.D., Lieutenant-Colonel, I.M.S., retired, aged 72.

Maynard.—On January 6, 1951, at his home, 159, Sussex Gardens, Hyde Park, London, W., Edwin Maynard, M.D., F.R.C.S., D.P.H.

Patterson.—On January 8, 1951, at 312, High Road, Ilford, Essex, Mary Minnie Patterson, L.M.S.S.A.

Pitt.—On January 3, 1951, at the National Heart Hospital, London, Clive Nelson Pitt, M.B., Ch.M., of 25, de Vere Gardens, and 86, Brook Street, London, W., formerly of Sydney, Australia.

Pratt.—On January 6, 1951, at 69a, Goldsmid Road, Tonbridge, Kent, Sybil Madeline Georgina Pratt, M.R.C.S., L.R.C.P., late of Mill Hill, London, N.W.

Sansom.—On January 2, 1951, John Raymond Eden Sansom, M.B., Ch.B., of Bell Hill, Bristol, aged 54.

Swain.—On January 6, 1951, at Easton-in-Gordano, Somerset, James Swain, C.B., C.B.E., M.D., M.S., F.R.C.S.

Wallace.—On January 6, 1951, at Filleigh, Chudleigh, Devon, Lewis Alexander Richard Wallace, M.B., late of Gloucester Court, Kew, Surrey, aged 85.

Wood.—On January 5, 1951, Francis Carter Wood, M.D., of 110, Lydecker Street, Englewood, New Jersey, U.S.A., aged 81.

Worthington.—On December 7, 1950, at Victoria, Vancouver Island, Canada, Charles Robert Worthington, B.Ch., formerly of Tonbridge, Kent, and Cam, Glos.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Crohn's Disease

Q.—*Does Crohn's disease occur in the colon—for example, in the splenic flexure—causing obstructive symptoms and showing as a filling defect in a radiograph following a barium enema? Is it likely that there will be much pyrexia in such a case? What investigations other than laparotomy might be carried out to differentiate between Crohn's disease and a malignant growth? If an anastomosis is done without resection of the diseased area, is it likely that antibiotics such as chloramphenicol will have any effects on the course of the disease?*

A.—Crohn's disease as such does not occur in the colon, although it is definitely not limited to the ileum in the small intestine. Somewhat similar pathological changes in the submucosa have been very occasionally reported as taking place in the colon, but not to the extent of producing obstruction or of causing a filling defect after a barium enema.

The patient's age is not stated, but the only other likely diagnosis apart from carcinoma is diverticulitis, and it is unlikely that evidence of this condition would be confined solely to the splenic flexure region. A mild pyrexia is usual with diverticulitis, but can also occur in carcinoma where obstruction is sufficient to produce a colitis proximal to the growth. A leucocyte count might give some indication of the degree of inflammation accompanying the condition.

If the patient's general condition permits it, a laparotomy (after such a barium enema result) would seem strongly indicated. The pre-operative use of the unabsorbable sulphonamides (e.g., phthalylsulphathiazole or succinylsulphathiazole) in large doses greatly reduces the risk of any subsequent surgical procedure that may be necessary. These drugs, and also the newer antibiotics, have a very definite effect on the bacterial flora of the large intestine, and should the condition happily be found at laparotomy to be inflammatory in origin (a difficult decision to make even when the mass is on view) they would certainly alleviate the condition.

Tar Burns

Q.—*What is the modern treatment for burns from hot tar? What is the best solvent for removing tar from the skin, particularly of the face? If a spot of tar falls into the eye, what is the first-aid and subsequent treatment?*

A.—The treatment of burns caused by tar, with which may be associated the allied substances pitch and bitumen, does not differ from that of burns due to other causes except in so far as certain modifications may be needed due to the propensity of these substances to adhere to the burned surface. In general the treatment adopted will depend on the depth of the burn and on its extent and situation. Burns of any depth may be caused, from the mildest erythema to complete skin destruction (whole skin loss or third-degree burn), according to the temperature of the tar, the amount falling on the skin, and the duration of the contact. The depth of burning should be ascertained by removing, if necessary, all or part of the adherent tar. This is best accomplished by waiting until the tar has cooled sufficiently to allow it to be peeled off, more or less in one piece. This is a relatively painless procedure, and in burns where epidermal separation has occurred the blistered epidermis will be removed with the tar.

Trichlorethylene will remove tar from the skin fairly satisfactorily, but considerable pain may be caused, particularly in superficial burns. Benzene and toluene would probably be better solvents for removing large amounts of tar, but would again be painful. Afterwards, benzene should be removed from the skin with acetone. All these solvents should be avoided on the face, especially in the region of the eyes. After removal of the tar the depth of the burn can be roughly ascertained by inspection. Superficial burns have a reddish-pink colour and a clearly intact capillary circulation, whilst deeper burns are paler, progressing to the white appearance of whole-skin-loss burns with an absence of capillary circulation. A further aid to determination of the depth of burning is the testing of the pin-prick sensation of the burned surface, whole-skin-loss burns being analgesic, partial-skin-loss burns hypoalgesic, and very superficial burns hyperalgesic (J. P. Bull and J. E. Lennard-Jones, *Clin. Sci.*, 1949, **8**, 155).

All except clearly whole-skin-loss burns are then best cleaned with a 1% cetrimide solution ("cetavlon") and dressed with penicillin cream and dry gauze. The dressing should be large enough completely to seal the burn from the air, and should incorporate cotton-wool to absorb any exudate. This dressing may be left in place for seven days or so if the bandage remains intact, but must be replaced if it becomes wet or displaced. If healing is not complete within three or four weeks it is probable that areas of whole skin loss are present and skin grafting will be required. Burns of the face are best treated after cleaning with cetrimide by frequent spraying with a penicillin-lactose powder and leaving uncovered. In burns of limited extent, such as small splash burns, in which it is certain that the burn is superficial, it is often inadvisable to remove the tar, as it acts as a cover to the burn until it heals. Burns diagnosed initially as having caused complete skin destruction are often amenable to immediate surgical excision and skin-grafting on the day of injury, and must be at once referred to hospital.

In the distillation of coal the first (low temperature) fraction contains about 1% phenol and 3% cresols, whilst ordinary road tar is said to contain about the same amount of phenol, from which bitumen and pitch are free. One authority has mentioned the risk of phenol absorption after the burn, but it seems that with concentrations of this order a very high proportion of the body surface would have to be covered with tar before the risk would be serious. Such injuries must be extremely rare, but in them the possibility should not be overlooked.

Tar rarely falls directly into the eye, because of the protective reflex of the lids. In lid burns the less first-aid treatment the better, immediate covering of the burn with a sterile dressing being sufficient. If tar actually enters the eye first-aid should be limited to immediate washing out with large amounts of water followed by the application of a sterile dressing. The subsequent treatment depends on whether the tar has burned the sclera or cornea. If the latter is involved instillation of homatropine is indicated to keep the pupil dilated, together with frequent irrigation with boric acid solutions. In purely scleral burns it is unnecessary to produce pupillary dilatation. Any tar adherent to the globe should be removed with a spud. The eye should be kept covered, and in extensive burns, and those also involving the eyelids, the fornices and outer surfaces of the lids may be packed after each irrigation with penicillin cream before a dressing is applied.

Treatment of Pediculosis

Q.—*What are the best methods of treating pediculosis?*

A.—Head louse infestations may be dealt with by the following procedure:

1. Application of a persistent insecticide to the hair, giving instructions that the hair should not be washed for a week.
2. Gift of a small quantity for use by other members of the infested person's family (if they are not available for treatment).
3. Reinspection after one to two weeks. Washing of the hair. Removal of nits by a fine-toothed metal comb (optional, as they should all be dead or hatched).
4. Second application of insecticide.

The following suitable insecticides are available from pharmacists: "gammexane" 0.2% (preferably as an aqueous suspension); D.D.T. 2% (as emulsion); lethane hair oil (*N.W.F.*).

Body louse infestations are much rarer and confined to people who do not regularly change their underwear. The simplest treatment is the liberal use of 10% D.D.T. powder, scattered among the underwear. This does not kill the eggs, but the powder persists long enough to destroy the young lice as they hatch out. For crab lice, two or three good applications of 10% D.D.T. powder should be made to the pubic hair at weekly intervals.

Treatment of Condyloma Acuminatum

Q.—*What is the treatment of condyloma acuminatum? A male patient, aged 37, has a profuse growth of cauliflower-like warts around the anus with one or two warts on the penis. The Kahn test is negative. Silver nitrate has been tried without success, and a 25% solution of podophyllin resin in liquid paraffin with only temporary effect. I wish to avoid surgical treatment if possible. What steps would you suggest?*

A.—There is no reliable alternative to treatment with podophyllin other than surgical removal. In the case described a further trial of podophyllin is advised. It is not unusual for large warts of this sort to need several applications at weekly intervals. If this fails the only treatment likely to succeed is surgical removal of the warts with scissors or curette under general anaesthesia, followed by cauterization of their base.

Congenital Aural Fistula

Q.—*I recently saw a baby with a tiny depression, about the size of the head of a pin, on the crus of the helix of the left ear. On the right ear, in an identical position, there was a small sinus which was discharging mucoid material. The mother informs me that these were first noticed by her when the child was brought home from hospital on the tenth day. What is this condition?*

A.—The description is that of a congenital aural fistula. Such fistulae are unilateral or bilateral and may be associated with other defects such as auricular appendages. The commonest site for the fistula is the anterior margin of the helix. The length of the sinus track is usually 5 to 7 mm. Figures given for their frequency in the normal population vary from 1 to 6%. The openings are probably the result of the failure of complete fusion of the six primary embryonal tubercles which form the external ear. The fistulae are usually symptomless, but they may become obstructed by desquamating epithelial cells and mucoid secretion and so become infected and form an abscess. The condition should, in fact, always be borne in mind when local suppuration occurs at this site. Treatment in an uncomplicated case is unnecessary, but if there is recurrent suppuration the sinus track should be excised.

Inheritance of Asthma

Q.—*I have been asked by a patient, who is asthmatic, whether there is any substance that his wife, while she is pregnant, could take to prevent hereditary asthma. I have not been able to trace any reference to such a substance, but I wonder if you could help.*

A.—There is no substance which can be given to a pregnant woman which influences whether or not her child will develop asthma. Unless there is a strong history of allergy on both sides of the family, the chance of any individual child developing asthma is small.

If there is a strong bilateral inheritance, the questioner might consider the advisability of the mother avoiding excessive eating of individual foods during pregnancy, as there is evidence that this has led to active sensitization *in utero*.

The Impotent Husband

Q.—*An athletic man of 46, resident in Kenya and the father of three young children, complains of a falling off in sexual efficiency, which has developed over a comparatively short time. The only illness to which he admits is dysentery some six years ago. Physical examination is negative, and I think it very unlikely that there is a psychological element in this case. What is the likely cause of the condition, and how should it be treated?*

A.—Without more precise information it is impossible to account for the patient's impotence. The majority of cases of impotence are psychogenic, and the responsible factors are often multiple—anxiety, loss of confidence, preoccupation with the state of erection at the start of intercourse, nervousness lest intercourse should result in economic difficulties owing to the birth of another child, emotional stresses between the husband and wife, fear that damage has been done to the genital organs by previous masturbation, and a score of other possible factors might be suggested.

As no precise diagnosis can be made, treatment must be along general lines. The patient must be repeatedly reassured that the genital organs are intact and told that the difficulties are only temporary. It is vital that the co-operation and understanding of the wife should be procured, because her attitude to her husband's failures is a determining factor. Middle-aged patients often benefit from small doses of thyroid, and injections of testosterone may be helpful, especially when they are made the occasion for more psychotherapy.

Fainting in the Surgery

Q.—*Is there any prophylactic for patients who habitually suffer from vasovagal attacks in doctors' or dentists' surgeries?*

A.—Vasovagal attacks are more likely to occur in some patients than in others, and it is very difficult to spot those liable before their first attacks. Therefore precautions should be taken in all patients, while special precautions should be taken in those who have had fainting attacks before. Fainting is much more likely to occur in the standing or sitting position, and procedures likely to produce fainting should therefore where possible be carried out with the patient horizontal. Should the patient show signs of an impending attack (pallor, sweating, over-breathing, and a slow pulse) the patient should be made to lie down.

No drug is known which is likely to prevent such attacks occurring.

Correction.—In the third paragraph, lines 1 and 2, of Dr. D. P. Jones's article, "Methoin in the Treatment of Epilepsy" (January 13, p. 64), the chemical name for "dilantal" was erroneously given as sodium diphenylhydantoinate. This should have read "a combination of 'mesontoin' and phenobarbitone."

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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